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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification:** **C12N 15/12, C07K 14/705, G01N 33/68**

A2

(11) **International Publication Number:** **WO 00/70044**

(43) **International Publication Date:** 23 November 2000 (23.11.2000)

(21) **International Application Number:** PCT/US00/12383

(22) **International Filing Date:** 08 May 2000 (08.05.2000)

(30) **Priority Data:**
60/134,063 13 May 1999 (13.05.1999) US
60/137,547 04 June 1999 (04.06.1999) US

(60) **Parent Application or Grant**
THE JOHNS HOPKINS UNIVERSITY [/]; (). MITTMAN, Scott [/]; (). AGNEW, William, S. [/]; (). MITTMAN, Scott [/]; (). AGNEW, William, S. [/]; (). KAGAN, Sarah, A. ; ().

Published

(54) **Title: HUMAN BRAIN T CALCIUM CHANNEL ALPHA-SUBUNIT SPLICE VARIANTS**

(54) **Titre: VARIANTS EPISSES DE LA SOUS-UNITE ALPHA DES CANAUX CALCIUM T DANS LE CERVEAU HUMAIN**

(57) Abstract

The structures of CACNA1G and CACNA1I, the genes encoding the human brain T Ca2+¿ channel 'alpha'¿1G and 'alpha'¿1I subunits, respectively, were determined by comparison of polymerase chain reaction-amplified brain cDNA and genomic sequences. CACNA1G consists of at least 38 exons spanning at least 66,490 basepairs of chromosome 17q22. Alternative splicing of the RNA occurs at six sites: cassette exons 14, 26, 34 and 35, an internal donor in exon 25 and protein-coding intron 38B. Additionally, the RNA can be polyadenylated at either of two sites. Alternative splicing of CANCA1G RNA may lead to expression of as many as 64 distinct protein products, ranging from 2,171 to 2,377 amino-acids residues, with as many as 45 potential phosphorylation sites. CACNA1I consists of at least 37 exons spanning at least 116,390 basepairs of chromosome 22q12.3-13.2. Alternative splicing of the gene occurs at three sites: cassette exon 9, an alternative acceptor in exon 33 and mutually-exclusive 3' exons 36B and 37. Alternative splicing of CANCA1I RNA may lead to expression of as many as 8 distinct protein products, ranging from 1,968 to 2, 223 amino-acids residues, with as many as 28 potential phosphorylation sites. Molecular diversity generated by alternative splicing and post-translation modification of these and other members of the T 'alpha'¿1 subunit gene family may account for the observed heterogeneity of T currents in central neurons.

(57) Abrégé

Dans cette invention on a déterminé les structures de CACNA1G et de CACNA1I, gènes codant les sous-unités 'alpha'¿1G et 'alpha'¿1I, respectivement, du canal T Ca2+¿ dans le cerveau humain, en comparant des ADNc du cerveau amplifiés par PCR et des séquences génomiques. CACNA1G est constitué d'au moins 38 exons recouvrant au moins 66 490 paires de base du chromosome 17q22. L'épissage alternatif de l'ARN a lieu dans six sites: exons de cassette 14, 26, 34 et 35, donneur interne dans l'exon 25 et intron 38B codant des protéines. En outre, l'ARN peut être polyadénylé dans n'importe lequel de ces deux sites. L'épissage alternatif d'ARN CACNA1G peut mener à l'expression de jusqu'à 64 produits protéiques distincts, compris entre les résidus d'acides aminés 2171 et 2377, avec jusqu'à 45 sites potentiels de phosphorylation. CACNA1I consiste d'au moins 37 exons recouvrant au moins 116 390 paires de base du chromosome 22q12.3-13.2. L'épissage alternatif de l'ARN a lieu dans trois sites: exon de cassette 9, accepteur alternatif dans l'exon 33 et introns 36B et 37 de 3' s'excluant mutuellement. L'épissage alternatif d'ARN CACNA1I peut mener à l'expression de jusqu'à 8 produits protéiques distincts, compris entre les résidus d'acides aminés 1968 et 2223, avec jusqu'à 38 sites potentiels de phosphorylation. La diversité moléculaire, générée par l'épissage alternatif et la modification post-traductionnelle de ces membres et d'autres membres de la famille de gènes de sous-unité 'alpha'¿1G de T, peut refléter l'hétérogénéité observée des courants T dans les neurones centraux.

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(11) International Publication Number: **WO 00/70044**

(43) International Publication Date: 23 November 2000 (23.11.00)

(21) International Application Number: PCT/US00/12383

(22) International Filing Date: 8 May 2000 (08.05.00)

(30) Priority Data:

60/134,063	13 May 1999 (13.05.99)	US
60/137,547	4 June 1999 (04.06.99)	US

(71) Applicant *(for all designated States except US)*: THE JOHNS HOPKINS UNIVERSITY [US/US]; 111 Market Place, Baltimore, MD 21201 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MITTMAN, Scott [US/US]; The Johns Hopkins University, 111 Market Place, Baltimore, MD 21201 (US). AGNEW, William, S. [US/US]; The Johns Hopkins University, 111 Market Place, Baltimore, MD 21201 (US).

(74) Agents: KAGAN, Sarah, A. et al.; Banner & Witcoff, Ltd., Eleventh Floor, 1001 G Street, N.W., Washington, DC 20001–4597 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

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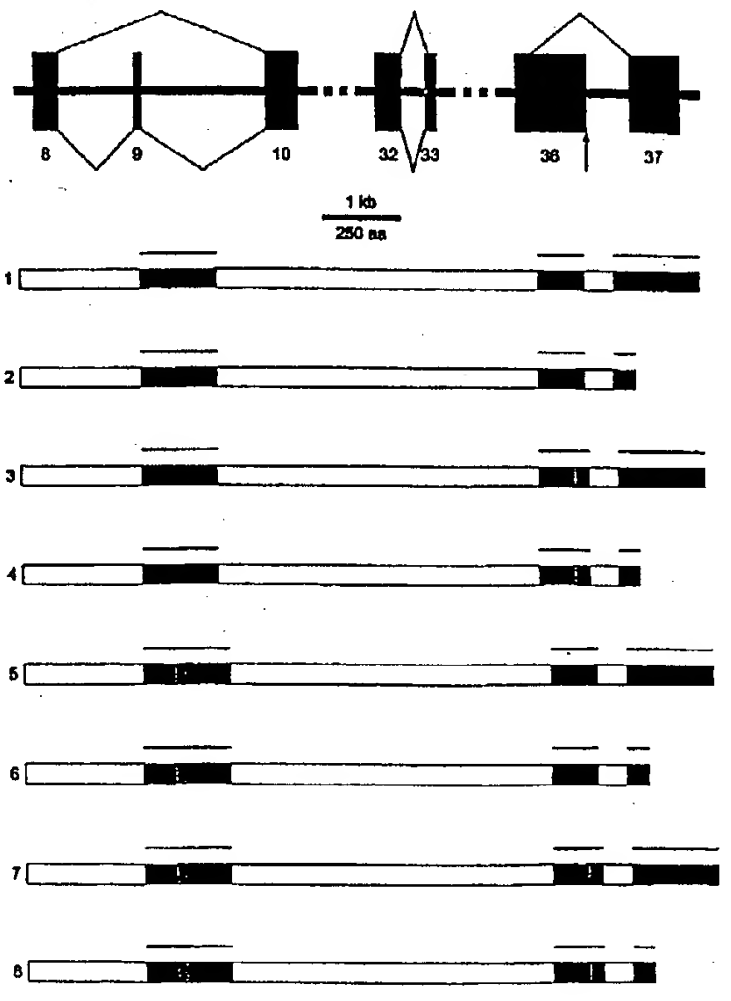
The structures of *CACNA1G* and *CACNA1I*, the genes encoding the human brain T Ca^{2+} channel α_{1G} and α_{1I} subunits, respectively, were determined by comparison of polymerase chain reaction–amplified brain cDNA and genomic sequences. *CACNA1G* consists of at least 38 exons spanning at least 66,490 basepairs of chromosome 17q22. Alternative splicing of the RNA occurs at six sites: cassette exons 14, 26, 34 and 35, an internal donor in exon 25 and protein–coding intron 38B. Additionally, the RNA can be polyadenylated at either of two sites. Alternative splicing of *CANCA1G* RNA may lead to expression of as many as 64 distinct protein products, ranging from 2,171 to 2,377 amino–acids residues, with as many as 45 potential phosphorylation sites. *CACNA1I* consists of at least 37 exons spanning at least 116,390 basepairs of chromosome 22q12.3–13.2. Alternative splicing of the gene occurs at three sites: cassette exon 9, an alternative acceptor in exon 33 and mutually–exclusive 3' exons 36B and 37. Alternative splicing of *CANCA1I* RNA may lead to expression of as many as 8 distinct protein products, ranging from 1,968 to 2,223 amino–acids residues, with as many as 28 potential phosphorylation sites. Molecular diversity generated by alternative splicing and post–translation modification of these and other members of the T α_1 subunit gene family may account for the observed heterogeneity of T currents in central neurons.



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Description

HUMAN BRAIN T CALCIUM CHANNEL ALPHA-SUBUNIT SPLICE VARIANTS

This invention was made using funds from the U.S. government. Under the terms of NIH grants K08NS01939 and P50HL52307, the government may retain certain rights in the invention.

TECHNICAL FIELD OF THE INVENTION

This invention is related to ion channels. In particular, it is related to ion channels related to brain function.

BACKGROUND OF THE INVENTION

Voltage-dependent calcium channels are involved in both coupling electrical activity to calcium influx and contributing to membrane properties. Low voltage-activated (LVA) calcium channels activate at potentials near the resting membrane potential. LVA participate in spike-induced calcium entry and allow calcium influx at potentials below threshold. LVA calcium channels also are involved in subthreshold membrane fluctuations. LVA calcium channel dysfunction is implicated in epileptiform activity. Moreover, these channels are targets for antiepileptic drugs.

T-type (transient) properties in neurons include low voltage activation, strongly voltage-dependent kinetics, rapid inactivation, slow deactivation, and small single-channel conductance.

Recently, a subfamily of genes (designated Ca_v3) has been discovered encoding α_1 subunits that are ~ 30% homologous to HVA subunit genes in their putative membrane-spanning regions.

T currents are a diverse class of Ca^{2+} current characterized by a low voltage threshold for activation. Proposed functions include generation of low-threshold spikes that lead to bursting, promotion of voltage oscillations, boosting of Ca^{2+} entry and synaptic potentiation. T currents may be the targets of succinimides and related compounds administered in the treatment of absence epilepsy. Recently, cDNA sequences of three T α_1 subunits, rat α_{1G} and α_{1I} and human α_{1H}, have been reported.

Ca^{2+} channel α_1 subunits are encoded by at least 10 genes falling into three subfamilies: ABE, SCDF and GHI[1]. Alternative splicing of α_1 RNAs generates further molecular diversity. There is a need in the art for identifying the different splice forms of the calcium channel subunits, so that they can be used as targets in drug discovery and development programs.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an isolated and purified α_{1G} subunit of human brain T calcium channel.

It is an object of the present invention to provide an isolated and purified nucleic acid encoding the α_{1G} subunit.

It is an object of the present invention to provide an isolated and purified α_{1I} subunit of human brain T calcium channel.

It is an object of the present invention to provide an isolated and purified nucleic acid encoding the α_{1I} subunit.

It is another object of the present invention to provide an isolated and purified nucleic acid comprising an exon of a human brain T calcium channel alpha subunit.

Another object of the invention is to provide an isolated and purified polypeptide which comprises a translated exon of a human brain T calcium channel.

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1 The gene encoding the subunit α_{1X}, where X is A - I, or S, is denoted *CACNA1X*. Alternative names for the SCDF and GHI subfamilies are L and T, respectively.

Another object of the invention is to provide expression vectors and host cells for expressing the subunits of human brain T calcium channel.

Another object of the invention is to provide a method to identify candidate drugs for treating epilepsy.

These and other objects of the invention are achieved by one or more of the embodiments described below. In one embodiment an isolated and purified α_{1G} subunit of human brain T calcium channel is provided. The subunit is selected from splice variants 1-64 as shown in Table 1.

According to another object of the invention an isolated and purified nucleic acid encoding the α_{1G} subunit is provided.

According to still another object of the invention an isolated and purified polypeptide is provided which comprises a translated exon selected from the group consisting of 1-38D as shown in Table 2.

Another embodiment of the invention is an isolated and purified nucleic acid which comprises an exon selected from the group consisting of 1-38D as shown in Table 2.

Still another embodiment of the invention is an isolated and purified α_{1I} subunit of human brain T calcium channel selected from splice variants 1-8 as shown in Table 3.

The present invention also provides an isolated and purified polypeptide which comprises a translated exon selected from the group consisting of 1-37 as shown in Table 4.

According to another aspect of the invention an isolated and purified nucleic acid is provided which comprises an exon selected from the group consisting of 1-37 as shown in Table 4.

Vectors and host cells which contain and/or express any of the nucleic acids, polypeptides or proteins described above are also contemplated as part of the present invention.

Other embodiments of the invention are methods to identify candidate drugs for treating epilepsy. A host cell containing a nucleic acid encoding an α_{1G} or α_{1I} subunit or exon is contacted with a test substance. Uptake by the cell of calcium ions is measured. A test substance which inhibits the uptake by the cell of calcium ions is identified as a candidate drug for treating epilepsy.

These and other embodiments of the invention which will be described in more detail below, and which will be evident to those of ordinary skill in the art upon reading the disclosure, provide the art with new drug discovery targets which can form the basis of a drug screening program.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1. Map of *CACNA1I* and α_{1I} cDNA. In the genomic map (bottom), exons are indicated by vertical bars and introns by the connecting horizontal line. The smallest exons are not to scale due to the minimum line thickness required for printing. In the cDNA map (middle), constitutively-spliced, odd-numbered exons are black and even-numbered exons, gray. Alternatively-processed exons (or portions of exons) are colored as follows: 9 – red, 33A – orange, 36B – green. The thinner portions of exons 1 and 36 represent the 5′ and 3′ untranslated regions, respectively. Selected exons are labeled to facilitate counting. Black bars above this cDNA map indicate relative PCR product locations. Four of the bars are interrupted by a thin line to indicate portions deleted by alternative splicing. Exon 37 (blue) is mutually exclusive with exon 36, requiring a separate representation of the 3′ end of the cDNA, at the top. Only a small portion of the exon 37 3′ UTR has been amplified and sequenced. Two of the PCR products containing portions of exon 37 are represented as black bars above the partial cDNA map. The starred scale bar equals 1 kb for PCR products and the cDNA maps and 15 kb for the genomic map.

Fig. 2. Schematic of the predicted α_{1I} protein. Each aa residue is represented by a small circle. In the large cytoplasmic and extracellular loops, a full up-down cycle measures 100 residues. Main features of the topology are labeled in large type and described in the text. Portions of the protein derived from odd-numbered exons are labeled in small type. A similarity score was computed for each residue from alignments of the aa sequence of each α_{1I} exon with the sequences of the homologous human α_{1G} and α_{1H} exons by iterative pairwise use of gap with default parameters. *Pipe*, *colon*, *period* and *space* similarity symbols were assigned numerical values of 3, 2, 1 and 0, respectively; α_{1I} vs. α_{1G} and α_{1I} vs. α_{1H} scores for an individual α_{1I} residue were added to yield a final score of 0 to 6. Residue identity in all three proteins produced a score of 6; pairing of an α_{1I} residue with unrelated amino acids in both alignments produced

a score of 0. Exons 9, 34 and 35 had no apparent α_{1G} or α_{1H} homologues; these residues are uncolored. Exon 16 had only an α_{1H} homologue and exons 33 and 37 had only α_{1G} homologues; the maximum possible similarity score for these exons is 3. Portions of the protein deleted by alternative splicing have a light blue background. Mutually exclusive exons 36B (7 aa) and 37 (214 aa) are side-by-side. Extracellular cysteines, potential N-glycosylation and phosphorylation sites and the location of splice sites (mapped to the protein product) are indicated by the appropriate symbols. Symbol colors have the following meanings: black – conserved among all human α_1 subunits; purple – conserved within 3 aa residues in the multiple sequence alignment of all human α_1 subunits; blue – conserved among the human ABE and GHI subfamilies; green – conserved among all human T α_1 subunits; brown – also present in human α_{1H}; orange – also present in human α_{1G}; pink – unique to α_{1I}. PKA: cyclic-nucleotide-dependent protein kinase phosphorylation site, PKC: protein kinase C phosphorylation site, CKII: casein kinase II phosphorylation site, Tyr: tyrosine kinase phosphorylation site. One residue in the C-terminus was identified as a potential site for phosphorylation by both PKA and CKII; another was identified as a potential site for phosphorylation by both PKA and PKC.

Fig. 3. Map of *CACNA1G* and the α_{1G} cDNA. In the genomic map (bottom), exons are indicated by vertical bars and introns by the connecting horizontal line. The smallest exons are not to scale due to the minimum line thickness required for printing. In the cDNA map (middle), constitutively-spliced, odd-numbered exons are gray and even-numbered exons, black. Alternatively-processed exons (or portions of exons) are colored as follows: 14 – olive, 25B – red, 26 – blue, 34 – light green, 35 – orange, 38B – dark green, 38D – purple. The thinner portions of exons 1 and 38 represent the 5′ and 3′ untranslated regions, respectively. Selected exons are labeled to facilitate counting. Black bars at the top of the figure indicate PCR product locations relative to the cDNA map. Nine of the bars are interrupted by a thin line to indicate portions deleted by alternative splicing. Red bars (labeled with GenBank accession numbers) represent infant brain cDNA clone ESTs. For one clone, only a 3′ EST has been reported. Thin lines indicate portions deleted by alternative splicing

and dashed lines indicate unsequenced portions. The starred scale bar equals 1 kb for PCR products and the cDNA map and 10 kb for the genomic map.

Fig. 4. Schematic of predicted α_{1G} proteins. Each aa residues is represented by a small circle. In the large cytoplasmic and extracellular loops, a full up-down cycle measures 100 residues. Main features of the topology are labeled in large type and described in the text. Portions of the protein involved in alternative splicing have a blue background. These and portions derived from odd-numbered exons are labeled in small type. A similarity score was computed for each residue from alignments of the aa sequence of each α_{1G} exon with the sequences of the homologous human α_{1H} (unpublished observations) and α_{1I} (submitted) exons by iterative pairwise use of **gap** (Genetics Computer Group, Wisconsin Package Version 9.0) with default parameters. *Pipe*, *colon*, *period* and *space* similarity symbols were assigned numerical values of 3, 2, 1 and 0, respectively; α_{1G} *vs.* α_{1H} and α_{1G} *vs.* α_{1I} scores for an individual α_{1G} residue were added to yield a final score of 0 to 6. Residue identity in all three proteins produced a score of 6; pairing of an α_{1G} residue with unrelated amino acids in both alignments produced a score of 0. Exons 14, 16, 26, 35 and 38 had no apparent α_{1H} or α_{1I} homologues; these residues are uncolored. Exon 36 and the C-terminal half of exon 8 had only α_{1H} homologues and exon 34 had only an α_{1I} homologue; the maximum possible similarity score for these regions is 3. Splice sites, extracellular cysteines and potential *N*-glycosylation and phosphorylation sites identified with PROSITE are indicated by the appropriate symbols. Symbol colors have the following meanings: black – conserved among all human α_1 subunits, purple – conserved within 3 aa residues in the multiple sequence alignment of all human α_1 subunits, blue – conserved among the human ABE and GHI subfamilies, green – conserved among all human T α_1 subunits, brown – also present in human α_{1I}, orange – also present in human α_{1H}, pink – unique to α_{1G}. PKA: cyclic-nucleotide-dependent protein kinase phosphorylation site, PKC: protein kinase C phosphorylation site, CKII: casein kinase II phosphorylation site, Tyr: tyrosine kinase phosphorylation site. One residue in ID1-2 was identified as a potential site for phosphorylation by both PKA and PKC.

Fig. 5 is a schematic diagram of the RNA processing leading to the 8 α_{1I} variants.

DETAILED DESCRIPTION OF THE INVENTION

The human brain T calcium channel α_{1G} subunit gene, *CACNA1G*, has now been discovered to consist of 38 protein-coding exons. Alternative processing of the gene transcript allows this single gene to code for sixty-four distinct α_{1G} protein products. In Table 2, each exon or portion of an exon is listed. In Table 1, the component exons of individual splice variants are described. These two tables are sufficient for a complete description of the newly discovered compositions.

Table 1 lists the component exons of the 64 α_{1G} protein products. Only the missing portions of each variant are noted in the description; the symbol " Δ" denotes deletion of the exon following the symbol. Thus, variant 1 consists of all exons save 14, 25B, 26, 34, 35 and 38B; in other words, exons 1 – 13, 15- 24, 25A, 27 – 33, 36 – 37, 38A and 38C are concatenated to form the protein. The final column lists the number of aa residues in each variant.

Table 1. α_{1G} Splice Variants

Variant	Description	Exon 14	Exon 25B	Exon 26	Exon 34	Exon 35	Exon 38B	Length (aa)
1	Δ14Δ25BΔ26Δ34Δ35Δ38B	—	—	—	—	—	—	2164
2	Δ14Δ25BΔ26Δ34Δ35	—	—	—	—	—	+	2243
3	Δ14Δ25BΔ26Δ34Δ38B	—	—	—	—	+	—	2209
4	Δ14Δ25BΔ26Δ34	—	—	—	—	+	+	2288
5	Δ14Δ25BΔ26Δ35Δ38B	—	—	—	+	—	—	2212
6	Δ14Δ25BΔ26Δ35	—	—	—	+	—	+	2291
7	Δ14Δ25BΔ26Δ38B	—	—	—	+	+	—	2257
8	Δ14Δ25BΔ26	—	—	—	+	+	+	2336

		2182	2261	2227	2306	2230	2309	2275	2354	2171
9	Δ14Δ25BΔ34Δ35Δ38B	—	—	—	—	+	+	+	+	—
10	Δ14Δ25BΔ34Δ35	—	—	—	—	+	+	+	+	—
11	Δ14Δ25BΔ34Δ38B	—	—	—	—	+	+	+	+	—
12	Δ14Δ25BΔ34	—	—	—	—	+	+	+	+	—
13	Δ14Δ25BΔ35Δ38B	—	—	+	+	—	—	—	—	+
14	Δ14Δ25BΔ35	—	—	+	+	—	—	—	—	+
15	Δ14Δ25BΔ38B	—	—	+	+	—	—	—	—	+
16	Δ14Δ25B	—	—	+	+	—	—	—	—	+
17	Δ14Δ26Δ34Δ35Δ38B	—	—	+	+	—	—	—	—	+

	2250	2216	2295	2219	2298	2264	2343	2189	2268
18	Δ14Δ26Δ34Δ35	—	—	—	—	+	+	+	+
19	Δ14Δ26Δ34Δ38B	—	—	—	—	+	+	+	+
20	Δ14Δ26Δ34	—	—	—	—	+	+	+	+
21	Δ14Δ26Δ35Δ38B	—	—	—	—	+	+	+	+
22	Δ14Δ26Δ35	—	—	—	—	+	+	+	+
23	Δ14Δ26Δ38B	—	—	—	—	+	+	+	+
24	Δ14Δ26	—	—	—	—	+	+	+	+
25	Δ14Δ34Δ35Δ38B	—	—	—	—	+	+	+	+
26	Δ14Δ34Δ35	—	—	—	—	+	+	+	+

27	Δ14Δ34Δ38B	—	—	—	—	—	—	—
28	Δ14Δ34	—	+	—	+	—	+	—
29	Δ14Δ35Δ38B	—	—	+	+	—	—	+
30	Δ14Δ35	—	+	+	+	—	—	—
31	Δ14Δ38B	—	+	+	+	—	—	—
32	Δ14	—	+	+	+	—	—	—
33	Δ25BΔ26Δ34Δ35Δ38B	+	—	—	—	+	—	—
34	Δ25BΔ26Δ34Δ35	+	—	—	—	—	+	—
35	Δ25BΔ26Δ34Δ38B	+	—	—	—	—	—	+

36	Δ25BΔ26Δ34	+	—	+	—	+	—	+
37	Δ25BΔ26Δ35Δ38B	+	—	—	+	+	—	+
38	Δ25BΔ26Δ35	+	—	—	+	+	—	—
39	Δ25BΔ26Δ38B	+	—	—	+	—	+	+
40	Δ25BΔ26	+	—	—	+	—	+	—
41	Δ25BΔ34Δ35Δ38B	+	—	—	+	—	—	+
42	Δ25BΔ34Δ35	+	—	—	+	—	—	—
43	Δ25BΔ34Δ38B	+	—	—	—	+	+	+
44	Δ25BΔ34	+	—	—	—	+	+	—

	2253	2332	2298	2377	2194	2273	2239	2318	2242
45	Δ25BΔ35Δ38B	+	+	+	+	+	+	+	+
46	Δ25BΔ35	+	+	+	+	+	+	+	+
47	Δ25BΔ38B	+	+	+	+	+	+	+	+
48	Δ25B	+	+	+	+	+	+	+	+
49	Δ26Δ34Δ35Δ38B	+	+	+	+	+	+	+	+
50	Δ26Δ34Δ35	+	+	+	+	+	+	+	+
51	Δ26Δ34Δ38B	+	+	+	+	+	+	+	+
52	Δ26Δ34	+	+	+	+	+	+	+	+
53	Δ26Δ35Δ38B	+	+	+	+	+	+	+	+

	2321	2287	2366	2212	2291	2257	2336	2260	2339
54	Δ26Δ35	+	—	+	—	+	—	+	—	+
55	Δ26Δ38B	—	+	+	—	—	+	+	—	—
56	Δ26	+	+	+	—	—	—	—	+	+
57	Δ34Δ35Δ38B	—	—	—	+	+	+	+	+	+
58	Δ34Δ35	+	+	+	+	+	+	+	+	+
59	Δ34Δ38B	+	+	+	+	+	+	+	+	+
60	Δ34	+	+	+	+	+	+	+	+	+
61	Δ35Δ38B	+	+	+	+	+	+	+	+	+
62	Δ35	+	+	+	+	+	+	+	+	+

2305	2384
—	+
+	+
+	+
+	+
+	+
+	+
Δ38B	full
63	64

For each exon, the nucleotide sequence and the corresponding amino-acid (aa) sequence are listed in single-letter IUPAC code. Lower case letters in the aa sequences indicate that only two nucleotides of the codon belong to the exon (the codon is interrupted). A dash indicates a stop codon.

Table 2.

(SEQ ID NOs: 1 and 82) Exon 1 (constitutive)

atggacgaggaggaggatggagcgggcgccgaggagtcgggacagccccggagcttcatgcggctcaa
cgacctgtcgggggccgggggccggccgggccggggtcagcagaaaaggacccgggcagcgcggact
ccgaggcggaggggctgccgtacccggcgctggccccggtggttttcttctacttgagccaggacagc
cgcccgcggagctggtgtctccgcacggtctgtaaccc

MDEEEDGAGAEESGQPRSFMRLNDLSGAGGRPGPGSAEKDPGSADSEAEGLPYPALAPVVFFYLSQDS
RPRSWCLRTVCNp

(SEQ ID NOs: 2 and 83) Exon 2 (constitutive)

ctggtttgagcgcatcagcatgttggtcatccttctcaactgcgtgaccctgggcatgttccggccat
gcgaggacatcgcctgtgactcccagcgctgccggatcctgcag

WFERISMLVILLNCVTLGMFRPCEDIACDSQRCRILQ

(SEQ ID NOs: 3 and 84) Exon 3 (constitutive)

gcctttgatgacttcatctttgccttctttgccgtggagatggtggtgaagatggtggccttgggcat
ctttgggaaaaagtgttacctgggagacacttggaaccggcttgacttttcatcgtcatcgcagg

AFDDFIFAFFAVEMVVKMVALGIFGKKCYLGDTWNRLDFFIVIAg

(SEQ ID NOs: 4 and 85) Exon 4 (constitutive)

gatgctggagtactcgctggacctgcagaacgtcagcttctcagctgtcaggacagtccgtgtgctgc
gaccgctcagggccattaaccgggtgccca

MLEYSLDLQNVSFSAVRTVRVLRPLRAINRVP

(SEQ ID NOs: 5 and 86) Exon 5 (constitutive)

gcatgcgcatccttgtcacgttgctgctggatacgctgcccatgctgggcaacgtcctgctgctctgc
ttcttcgtcttcttcatcttcggcatcgtcggcgtccagctgtgggcagggctgcttcggaaccgatg
cttcctacctgagaatttcagcct

sMRILVTLLLDTLPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSl

(SEQ ID NOs: 6 and 87) Exon 6 (constitutive)

ccccctgagcgtggacctggagcgctattaccagacagagaacgaggatgagagccccttcatctgct
cccagccacgcgagaacggcatgcggtcctgcagaagcgtgcccacgctgcgcggggacgggggcggt
ggcccaccttgcggtctggactatgaggcctacaacagctccagcaacaccacctgtgtcaactggaa
ccagtactacaccaactgctcagcgggggagcacaaccccttcaagggcgccatcaactttgacaaca
ttggctatgcctggatcgccatcttccag

PLSVDLERYYQTENEDESPFICSQPRENGMRSCRSVPTLRGDGGGGPPCGLDYEAYNSSSNTTCVNWN
QYYTNCSAGEHNPFKGAINFDNIGYAWIAIFQ

(SEQ ID NOs: 7 and 88) Exon 7 (constitutive)

gtcatcacgctggagggctgggtcgacatcatgtactttgtgatggatgctcattccttctacaattt
catctacttcatcctcctcatcatc

VITLEGWVDIMYFVMDAHSFYNFIYFILLII

(SEQ ID NOs: 8 and 89) Exon 8 (constitutive)

gtgggctccttcttcatgatcaacctgtgcctggtggtgattgccacgcagttctcagagaccaagca
gcgggaaagccagctgatgcgggagcagcgtgtgcggttcctgtccaacgccagcaccctggctagct
tctctgagcccggcagctgctatgaggagctgctcaagtacctggtgtacatccttcgtaaggcagcc
cgcaggctggctcaggtctctcgggcagcaggtgtgcgggttgggctgctcagcagcccagcaccct
cgggggccaggagacccagcccagcagcagctgctctcgctcccaccgccgcctatccgtccaccacc
tggtgcaccaccaccaccaccatcaccaccactaccacctgggcaatgggacgctcagggcccccggg
gccagcccggagatccaggacagggatgccaatgggtcccgcaggctcatgctgccaccaccctcgac
gcctgccctctccgggggcccccccctggtggcgcagagtctgtgcacagcttctaccatgccgactgcc
acttagagccagtccgctgccaggcgcccccctcccaggtccccatctgaggcatccggcaggactgtg
ggcagcgggaaggtgtatcccaccgtgcacaccagccctccaccggagacgctgaaggagaaggcact
agtagaggtggctgccagctctgggcccccaaccctcaccagcctcaacatcccacccgggccctaca
gctccatgcacaagctgctggagacacagagtacag

VGSFFMINLCLVVIATQFSETKQRESQLMREQRVRFLSNASTLASFSEPGSCYEELLKYLVYILRKAA
RRLAQVSRAAGVRVGLLSSPAPLGGQETQPSSSCSRSHRRLSVHHLVHHHHHHHHHHYHLGNGTLRAPR
ASPEIQDRDANGSRRLMLPPPSTPALSGAPPGGAESVHSFYHADCHLEPVRCQAPPPRSPSEASGRTV
GSGKVYPTVHTSPPPETLKEKALVEVAASSGPPTLTSLNIPPGPYSSMHKLLETQST

(SEQ ID NOs: 9 and 90) Exon 9 (constitutive)

gtgcctgccaaagctcttgcaagatctccagcccttgcttgaaagcagacagtggagcctgtggtcca
gacagctgcccctactgtgcccgggccggggcaggggaggtggagctcgccgaccgtgaaatgcctga
ctcagacagcgaggcagtttatgagttcacacaggatgcccagcacagcgacctccgggacccccaca

gccggcggcaacggagcctgggcccagatgcagagcccagctctgtgctggccttctggaggctaatc
tgtgacaccttccgaaagattgtggacagcaagtactttggccggggaatcatgatcgccatcctggt
caacacactcagcatgggcatcgaataccacgagcag

gACQSSCKISSPCLKADSGACGPDSCPYCARAGAGEVELADREMPDSDSEAVYEFTQDAQHSDLRDPH
SRRQRSLGPDAEPSSVLAFWRLICDTFRKIVDSKYFGRGIMIAILVNTLSMGIEYHEQ

(SEQ ID NOs: 10 and 91) Exon 10 (constitutive)

cccgaggagcttaccaacgccctagaaatcagcaacatcgtcttcaccagcctctttgccctggagat
gctgctgaagctgcttgtgtatggtccctttggctacatcaagaatccctacaacatcttcgatggtg
tcattgtggtcatcag

PEELTNALEISNIVFTSLFALEMLLKLLVYGPFGYIKNPYNIFDGVIVVIs

(SEQ ID NOs: 11 and 92) Exon 11 (constitutive)

cgtgtgggagatcgtgggccagcaggggggcggcctgtcggtgctgcggaccttccgcctgatgcgtg
tgctgaagctggtgcgcttcctgccggcgctgcagcggcagctggtggtgctcatgaagaccatggac
aacgtggccaccttctgcatgctgcttatgctcttcatcttcatcttcag

VWEIVGQQGGGLSVLRTFRLMRVLKLVRFLPALQRQLVVLMKTMDNVATFCMLLMLFIFIFs

(SEQ ID NOs: 12 and 93) Exon 12 (constitutive)

catcctgggcatgcatctcttcggctgcaagtttgcctctgagcgggatggggacaccctgccagacc
ggaagaattttgactccttgctctgggccatcgtcactgtctttcag

ILGMHLFGCKFASERDGDTLPDRKNFDSLLWAIVTVFQ

(SEQ ID NOs: 13 and 94) Exon 13 (constitutive)

atcctgacccaggaggactggaacaaagtcctctacaatggtatggcctccacgtcgtcctgggcggc
cctttatttcattgccctcatgaccttcggcaactacgtgctcttcaatttgctggtcgccattctgg
tggagggcttccaggcggag

ILTQEDWNKVLYNGMASTSSWAALYFIALMTFGNYVLFNLLVAILVEGFQAE

(SEQ ID NOs: 14 and 95) Exon 14 (variable)

gaaatcagcaaacgggaagatgcgagtggacagttaagctgtattcagctgcctgtcgactcccaggg
g

EISKREDASGQLSCIQLPVDSQG

(SEQ ID NOs: 15 and 96) Exon 15 (constitutive)

ggagatgccaacaagtccgaatcagagcccgatttcttctcacccagcctggatggtgatggggacag
gaagaagtgcttggcct

GDANKSESEPDFFSPSLDGDGDRKKCLA

(SEQ ID NOs: 16 and 97) Exon 16 (constitutive)

tggtgtccctgggagagcacccggagctgcggaagagcctgctgccgcctctcatcatccacacggcc
gccacacccatgtcgctgcccaagagcaccagcacgggcctgggcgaggcgctgggccctgcgtcgcg
ccgcaccagcagcagcgggtcggcagagcctggggcggcccacgagatgaagtcaccg

lVSLGEHPELRKSLLPPLIIHTAATPMSLPKSTSTGLGEALGPASRRTSSSGSAEPGAAHEMKSP

(SEQ ID NOs: 17 and 98) Exon 17 (constitutive)

cccagcgcccgcagctctccgcacagcccctggagcgctgcaagcagctggaccagcaggcgctccag
ccggaacagcctcggccgtgcacccagcctgaagcggagaagcccaagtggagagcggcggtccctgt
tgtcgggagaaggccaggagagccaggatgaagaggagagctcagaagaggagcgggccagccctgcg
ggcagtgaccatcgccacaggggtccctggagcgggaggccaagagttcctttgacctgccagacac
actgcaggtgccagggctgcatcgcactgccagtggccgagggtctgcttctgagcaccaggactgca
atggcaagtcggcttcagggcgcctggcccgggccctgcggcctgatgacccccactggatggggat
gacgccgatgacgagggcaacctg

PSARSSPHSPWSAASSWTSRRSSRNSLGRAPSLKRRSPSGERRSLLSGEGQESQDEEESSEEERASPA
GSDHRHRGSLEREAKSSFDLPDTLQVPGLHRTASGRGSASEHQDCNGKSASGRLARALRPDDPPLDGD
DADDEGNL

(SEQ ID NOs: 18 and 99) Exon 18 (constitutive)

agcaaaggggaacgggtccgcgcgtggatccgagcccgactccctgcctgctgcctcgagcgagactc
ctggtcagcctacatcttccctcctcagtccag

SKGERVRAWIRARLPACCLERDSWSAYIFPPQSr

(SEQ ID NOs: 19 and 100) Exon 19 (constitutive)

gttccgcctcctgtgtcaccggatcatcacccacaagatgttcgaccacgtggtccttgtcatcatct
tccttaactgcatcaccatcgccatggagcgccccaaaattgacccccacagcgct

FRLLCHRIITHKMFDHVVLVIIFLNCITIAMERPKIDPHSA

(SEQ ID NOs: 20 and 101) Exon 20 (constitutive)

gaacgcatcttcctgaccctctccaattacatcttcaccgcagtctttctggctgaaatgacagtgaa
g

ERIFLTLSNYIFTAVFLAEMTVK

(SEQ ID NOs: 21 and 102) Exon 21 (constitutive)

gtggtggcactgggctggtgcttcggggagcaggcgtacctgcggagcagttggaacgtgctggacgg
gctgttggtgctcatctccgtcatcgacattctggtgtccatggtctctgacagcggcaccaagatcc
tgggcatgctgagggtgctgcggctgctgcggaccctgcgcccgctcag

VVALGWCFGEQAYLRSSWNVLDGLLVLISVIDILVSMVSDSGTKILGMLRVLRLLRTLRPLr

(SEQ ID NOs: 22 and 103) Exon 22 (constitutive)

ggtgatcagccgggcgcaggggctgaagctggtggtggagacgctgatgtcctcactgaaacccatcg
gcaacattgtagtcatctgctgtgccttcttcatcattttcggcatcttgggggtgcag

VISRAQGLKLVVETLMSSLKPIGNIVVICCAFFIIFGILGVQ

(SEQ ID NOs: 23 and 104) Exon 23 (constitutive)

ctcttcaaagggaagtttttcgtgtgccagggcgaggataccaggaacatcaccaataaatcggactg
tgccgaggccagttaccggtgggtccggcacaagtacaactttgacaaccttggccag

LFKGKFFVCQGEDTRNITNKSDCAEASYRWVRHKYNFDNLGQ

(SEQ ID NOs: 24 and 105) Exon 24 (constitutive)

gccctgatgtccctgttcgttttggcctccaaggatggttgggtggacatcatgtacgatgggctgga
tgctgtgggcgtggaccagcag

ALMSLFVLASKDGWVDIMYDGLDAVGVDQQ

(SEQ ID NOs: 25 and 106) Exon 25A (constitutive)

cccatcatgaaccacaacccctggatgctgctgtacttcatctcgttcctgctcattgtggccttctt
tgtcctgaacatgtttgtgggtgtggtggtggagaacttccacaagtgtcggcagcaccaggaggaag
aggaggcccggcggcgggaggagaagcgcctacgaagactggagaaaaagagaagga

PIMNHNPWMLLYFISFLLIVAFFVLNMFVGVVVENFHKCRQHQEEEEARRREEKRLRRLEKKRR

(SEQ ID NOs: 26 and 107) Exon 25B (variable)

gtaaggagaagcagatggctg

sKEKQMA

(SEQ ID NOs: 27 and 108 and 162) Exon 26 (variable)

atctaatgctggacgatgtaattgcttccggcagctcagccagcgctgcgtcag

nLMLDDVIASGSSASAAS (when follows exon 25A)

dLMLDDVIASGSSASAAS (when follows exon 25B)

(SEQ ID NOs: 28 and 109 and 163) Exon 27 (constitutive)

aagcccagtgcaaaccttactactccgactactcccgcttccggctcctcgtccaccacttgtgcacc
agccactacctggacctcttcatcacaggtgtcatcgggctgaacgtggtcaccatggccatggagca
ctaccagcagccccag

eAQCKPYYSDYSRFRLLVHHLCTSHYLDLFITGVIGLNVVTMAMEHYQQPQ (when it follows exon 25B or exon 26)

kAQCKPYYSDYSRFRLLVHHLCTSHYLDLFITGVIGLNVVTMAMEHYQQPQ (when it follows exon 25A)

(SEQ ID NOs: 29 and 110) Exon 28 (constitutive)

attctggatgaggctctgaagatctgcaactacatcttcactgtcatctttgtcttggagtcagtttt
caaacttgtggcctttggtttccgtcggttcttccaggacag

ILDEALKICNYIFTVIFVLESVFKLVAFGFRRFFQDr

(SEQ ID NOs: 30 and 111) Exon 29 (constitutive)

gtggaaccagctggacctggccattgtgctgctgtccatcatgggcatcacgctggaggaaatcgagg
tcaacgcctcgctgcccatcaaccccaccatcatccgcatcatgagggtgctgcgcattgcccgag

WNQLDLAIVLLSIMGITLEEIEVNASLPINPTIIRIMRVLRIAR

(SEQ ID NOs: 31 and 112) Exon 30 (constitutive)

tgctgaagctgctgaagatggctgtgggcatgcgggcgctgctggacacggtgatgcaggccctgccc
cag

vLKLLKMAVGMRALLDTVMQALPQ

(SEQ ID NOs: 32 and 113) Exon 31 (constitutive)

gtggggaacctgggacttctcttcatgttgttgttttcatctttgcagctctgggcgtggagctctt
tggagacctgg

VGNLGLLFMLLFFIFAALGVELFGDL

(SEQ ID NOs: 33 and 114) Exon 32 (constitutive)

agtgtgacgagacacacccctgtgagggcctgggccgtcatgccacctttcggaactttggcatggcc
ttcctaaccctcttccgagtctccacaggtgacaattggaatggcattatgaag

eCDETHPCEGLGRHATFRNFGMAFLTLFRVSTGDNWNGIMK

(SEQ ID NOs: 34 and 115) Exon 33 (constitutive)

gacaccctccgggactgtgaccaggagtccacctgctacaacacggtcatctcgcctatctactttgt
gtccttcgtgctgacggcccagttcgtgctagtcaacgtggtgatcgccgtgctgatgaagcacctgg
aggagagcaacaaggaggccaaggaggaggccgagctagaggctgagctggagctggagatgaagacc
ctcagccccagccccactcgccactgggcagcccttcctctggcctggggtcgagggccccgacag
ccccgacagccccaagcctggggctctgcacccagcggcccacgcgagatcagcctcccacttttccc
tggagcaccccacg

DTLRDCDQESTCYNTVISPIYFVSFVLTAQFVLVNVVIAVLMKHLEESNKEAKEEAELEAELELEMKT
LSPQPHSPLGSPFLWPGVEGPDSPDSPKPGALHPAAHARSASHFSLEHPT

(SEQ ID NOs: 35 and 116) Exon 34 (variable)

gacaggcagctgtttgacaccatatccctgctgatccagggctccctggagtgggagctgaagctgat
ggacgagctggcaggcccaggggccagccctctgccttcccttctgccccagcctgggaggctccg
acccacag

DRQLFDTISLLIQGSLEWELKLMDELAGPGGQPSAFPSAPSLGGSDPQ

(SEQ ID NOs: 36 and 117) Exon 35 (variable)

atccctctagctgagatggaggctctgtctctgacgtcagagattgtgtctgaaccgtcctgctctct
agctctgacggatgactctttgcctgatgacatgcacacactcttacttagtgccctggagagcaat

IPLAEMEALSLTSEIVSEPSCSLALTDDSLPDDMHTLLLSALESN

(SEQ ID NOs: 37 and 118) Exon 36 (constitutive)

atgcagccccaccccacggagctgccaggaccagacttactgactgtgcggaagtctggggtcagccg
aacgcactctctgcccaatgacagctacatgtgtcggcatgggagcactgccgaggggcccctgggac
acaggggctgggggctccccaaagctcagtcag

MQPHPTELPGPDLLTVRKSGVSRTHSLPNDSYMCRHGSTAEGPLGHRGWGLPKAQS

(SEQ ID NOs: 38 and 119) Exon 37 (constitutive)

gctccgtcttgtccgttcactcccagccagcagataccagctacatcctgcagcttcccaaagatgca
cctcatctgctccagccccacagcgccccaacctggggcaccatccccaaactgcccccaccaggacg
ctccccctttggctcagaggccactcaggcgccag

gSVLSVHSQPADTSYILQLPKDAPHLLQPHSAPTWGTIPKLPPPGRSPLAQRPLRRQ

(SEQ ID NOs: 39 and 120) Exon 38A (constitutive)

gcagcaataaggactgactccttggacgttcagggtctgggcagccgggaagacctgctggcagag

AAIRTDSLDVQGLGSREDLLAE

(SEQ ID NOs: 40 and 121) Exon 38B (variable)

gtgagtgggccctccccgcccctggcccgggcctactctttctggggccagtcaagtacccaggcaca
gcagcactcccgcagccacagcaagatctccaagcacatgaccccgccagccccttgcccaggcccag
aacccaactggggcaagggccctccagagaccagaagcagcttagagttggacacggagctgagctgg
atttcaggagacctcctgccccctggcggccag

VSGPSPPLARAYSFWGQSSTQAQQHSRSHSKISKHMTPPAPCPGPEPNWGKGPPETRSSLELDTELSW
ISGDLLPPGGQ

(SEQ ID NOs: 41 and 122) Exon 38C (constitutive)

gaggagcccccatccccacgggacctgaagaagtgctacagcgtggaggcccagagctgccagcgccggcctacgtc
tctattttattaaattaattgaatctagta

EEPPSPRDLKKCYSVEAQSCQRRPTSWLDEQRRHSIAVSCLDSGSQPHLGTDPSNLGGQPLGGPGSRP
KKKLSPPSITIDPPESQGPRTPPSPGICLRRRAPSSDSKDPLASGPPDSMAASPSPKKDVLSLSGLSS
DPADLDP-

(SEQ ID NO: 42) Exon 38D (variable)

tatgcgggatgtacgacattttgtgactgaagagacttgtttccttctacttttatgtgtctcagaat
atttttgaggcgaaggcgtctgtctcttggctattttaacctaaaataacagtctagttatattccct
cttcttgcaaagcacaagctgggaccgcgagcacattgcagccccaacggtggcccatcttcagcgga
gagcgagaaccattttggaaactgtaatgtaacttatttttccttaacctcgtcatcattttctgt
agggaaaaaaaaaagaaaaagaaaaaatgagattttacaagtgaaatggaacctttttatatatacat
acatacatatctatctatctatctatatatatataaaataaagtaattttcctaaataaaaa

Non-coding

The calcium channel α_{1I} subunit gene, *CACNA1I*, consists of 37 protein-coding exons. Alternative processing of the gene transcript allows this single gene to code for eight distinct α_{1I} protein products. In Table 4, each exon or portion of an exon is listed. In Table 3, the component exons of individual splice variants is described. These two tables are sufficient for a complete description of composition. The presumed RNA processing mechanisms giving rise to these variants are discussed below.

Table 3 lists the composition of the 8 α_{1I} protein products. Only the missing portions of each variant are noted in the description; the symbol "Δ" denotes deletion of the exon following the symbol. Thus, variant 1 consists of all exons save 9, 33A and 36B; in other words, exons 1 – 8, 10 – 32, 33B, 34 – 35, 36A and 37 are concatenated to form the protein. The final column lists the number of aa residues in each variant.

Table 3. α_{1I} Splice Variants

Variant	Description	Exon 9	Exon 33A	Exon 36B or 37	Length (aa)
1	Δ9Δ33AΔ36B	Δ	Δ	37	2175
2	Δ9Δ33AΔ37	Δ	Δ	36B	1968
3	Δ9Δ36B	Δ	+	37	2188
4	Δ9Δ37	Δ	+	36B	1981
5	Δ33AΔ36B	+	Δ	37	2210
6	Δ33AΔ37	+	Δ	36B	2003
7	Δ36B	+	+	37	2223
8	Δ37	+	+	36B	2016

For each exon, the nucleotide sequence and the corresponding amino-acid (aa) sequence are listed in single-letter IUPAC code. Lower case letters in the aa sequences indicate that only two nucleotides of the codon belong to the exon (the codon is interrupted). A dash indicates a stop codon.

TABLE 4

(SEQ ID NOs: 43 and 123) Exon 1 (constitutive)

atggctgagagcgcctccccgccctcctcatctgcagcagccccagccgctgagccaggagtcaccac
ggagcagcccggaccccggagccccccatcctccccgccaggcctggaggagcctctggatggagctg
atcctcatgtcccacacccagacctggcgcctattgccttcttctgcctgcgacagaccaccagcccc
cggaactggtgcatcaagatggtgtgcaaccc

MAESASPPSSSAAAPAAEPGVTTEQPGPRSPPSSPPGLEEPLDGADPHVPHPDLAPIAFFCLRQTTSP
RNWCIKMVCNp

(SEQ ID NOs: 44 and 124) Exon 2 (constitutive)

gtggtttgaatgtgtcagcatgctggtgatcctgctgaactgcgtgacacttggcatgtaccagccgt
gcgacgacatggactgcctgtccgaccgctgcaagatcctgcag

WFECVSMLVILLNCVTLGMYQPCDDMDCLSDRCKILQ

(SEQ ID NOs: 45 and 125) Exon 3 (constitutive)

gtctttgatgacttcatctttatcttctttgccatggagatggtgctcaagatggtggccctggggat
ttttggcaagaagtgctacctcggggacacatggaaccgcctggatttcttcatcgtcatggcagg

VFDDFIFIFFAMEMVLKMVALGIFGKKCYLGDTWNRLDFFIVMAg

(SEQ ID NOs: 46 and 126) Exon 4 (constitutive)

gatggtcgagtactccctggaccttcagaacatcaacctgtcagccatccgcaccgtgcgcgtcctga
ggcccctcaaagccatcaaccgcgtgccca

MVEYSLDLQNINLSAIRTVRVLRPLKAINRVP

(SEQ ID NOs: 47 and 127) Exon 5 (constitutive)

gtatgcggatcctggtgaacctgctcctggacacactgcccatgctggggaatgtcctgctgctctgc
ttctttgtcttcttcatctttggcatcataggtgtgcagctctgggcgggcctgctgcgtaaccgctg
cttcctggaggagaacttcaccat

sMRILVNLLLDTLPMLGNVLLLCFFVFFIFGIIGVQLWAGLLRNRCFLEENFTi

(SEQ ID NOs: 48 and 128) Exon 6 (constitutive)

acaaggggatgtggccttgcccccatactaccagccggaggaggatgatgagatgcccttcatctgct
ccctgtcgggcgacaatgggataatgggctgccatgagatccccccgctcaaggagcagggccgtgag
tgctgcctgtccaaggacgacgtctacgactttggggcggggcgccaggacctcaatgccagcggcct
ctgtgtcaactggaaccgttactacaatgtgtgccgcacgggcagcgccaacccccacaagggtgcca
tcaactttgacaacatcggttatgcttggattgtcatcttccag

QGDVALPPYYQPEEDDEMPFICSLSGDNGIMGCHEIPPLKEQGRECCLSKDDVYDFGAGRQDLNASGL
CVNWNRYYNVCRTGSANPHKGAINFDNIGYAWIVIFQ

(SEQ ID NOs: 49 and 129) Exon 7 (constitutive)

gtgatcactctggaaggctgggtggagatcatgtactacgtgatggatgctcactccttctacaactt
catctacttcatcctgcttatcata

VITLEGWVEIMYYVMDAHSFYNFIYFILLII

(SEQ ID NOs: 50 and 130) Exon 8 (constitutive)

gtgggctccttcttcatgatcaacctgtgcctcgttgtcatagcgacccagttctcggagaccaagca
acgggagcaccggctgatgctggagcagcggcagcgctacctgtcctccagcacggtggccagctacg
ccgagcctggcgactgctacgaggagatcttccagtatgtctgccacatcctgcgcaaggccaagcgc
cgcgccctgggcctctaccaggccctgcagagccggcgccaggccctgggcccggaggccccggcccc
cgccaaacctgggccccacgccaaggagccccggcactacc

VGSFFMINLCLVVIATQFSETKQREHRLMLEQRQRYLSSSTVASYAEPGDCYEEIFQYVCHILRKAKR
RALGLYQALQSRRQALGPEAPAPAKPGPHAKEPRHY

(SEQ ID NOs: 51 and 131) Exon 9 (variable)

atgggaagactaagggtcagggagatgaagggagacatctcggaagccggcattgccagactttgcat
gggcctgcctcccctggaaatgatcactcgggaagag

hGKTKGQGDEGRHLGSRHCQTLHGPASPGNDHSGR

(SEQ ID NOs: 52 and 132 and 164) Exon 10 (constitutive)

agctgtgcccgcaacatagccccctggatgcgacgccccacaccctggtgcagcccatccccgccacg
ctggcttccgatcccgccagctgcccttgctgccagcatgaggacggccggcggccctcgggcctggg
cagcaccgactcgggccaggagggctcgggctccgggagctccgctggtggcgaggacgaggcggatg
gggacggggcccggagcagcgaggacggagcctcctcagaactggggaaggaggaggaggaggaggag
caggcggatggggcggtctggctgtgcggggatgtgtggcgggagacgcgagccaagctgcgcggcat
cgtggacagcaagtacttcaaccggggcatcatgatggccatcctggtcaacaccgtcagcatgggca
tcgagcaccacgagcag

eLCPQHSPLDATPHTLVQPIPATLASDPASCPCCQHEDGRRPSGLGSTDSGQEGSGSGSSAGGEDEAD
GDGARSSEDGASSELGKEEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIMMAILVNTVSMG
IEHHEQ (when it follows exon 9)

qLCPQHSPLDATPHTLVQPIPATLASDPASCPCCQHEDGRRPSGLGSTDSGQEGSGSGSSAGGEDEAD
GDGARSSEDGASSELGKEEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIMMAILVNTVSMG
IEHHEQ (when if follows exon 8)

(SEQ ID NOs: 53 and 133) Exon 11 (constitutive)

ccggaggagctgaccaacatcctggagatctgcaatgtggtcttcaccagcatgtttgccctggagat
gatcctgaagctggctgcatttgggctcttcgactacctgcgtaacccctacaacatcttcgacagca
tcattgtcatcatcag

PEELTNILEICNVVFTSMFALEMILKLAAFGLFDYLRNPYNIFDSIIVIIs

(SEQ ID NOs: 54 and 134) Exon 12 (constitutive)

catctgggagatcgtggggcaggcggacggtgggctgtcggtgctgcggaccttccggctgctgcgcg
tgctgaaactggtgcgcttcatgcctgccctgcggcgccagctcgtggtgctcatgaagaccatggac
aacgtggccaccttctgcatgctgctcatgctcttcatcttcatcttcag

IWEIVGQADGGLSVLRTFRLLRVLKLVRFMPALRRQLVVLMKTMDNVATFCMLLMLFIFIFs

(SEQ ID NOs: 55 and 135) Exon 13 (constitutive)

catccttgggatgcatatttttggctgcaagttcagcctccgcacggacactggagacacggtgcccg
acaggaagaacttcgactccctgctgtgggccatcgtcactgtgttccag

ILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLWAIVTVFQ

(SEQ ID NOs: 56 and 136) Exon 14 (constitutive)

atcctcacccaggaggactggaacgtcgttctctacaatggcatggcctccacttctccctgggcctc
cctctactttgtcgccctcatgaccttcggcaactatgtgctcttcaacctgctggtggccatcctgg
tggagggcttccaggcggag

ILTQEDWNVVLYNGMASTSPWASLYFVALMTFGNYVLFNLLVAILVEGFQAE

(SEQ ID NOs: 57 and 137) Exon 15 (constitutive)

ggtgacgccaatcgctcctactcggacgaggaccagagctcatccaacatagaagagtttgataagct
ccaggaaggcctggacagcagcggag

GDANRSYSDEDQSSSNIEEFDKLQEGLDSSG

(SEQ ID NOs: 58 and 138) Exon 16 (constitutive)

atcccaagctctgcccaatccccatgaccccaatgggcacctggaccccagtctcccactgggtggg
cacctaggtcctgctggggctgcgggacctgccccccgactctcactgcagccggaccccatgctggt
ggccctgggctcccgaaagagcagtgtcatgtctctagggaggatgagctatgaccagcgctccctg

dPKLCPIPMTPNGHLDPSLPLGGHLGPAGAAGPAPRLSLQPDPMLVALGSRKSSVMSLGRMSYDQRSL

(SEQ ID NOs: 59 and 139) Exon 17 (constitutive)

tccagctcccggagctcctactacgggccatggggccgcagcgcggcctgggccagccgtcgctccag
ctggaacagcctcaagcacaagccgccgtcggcggagcatgagtccctgctctctgcggagcgcggcg
gcggcgcccgggtctgcgaggttgccgcggacgaggggccgccgcgggccgcacccctgcacacccca
cacgcccaccacattcatcacgggccccatctggcgcaccgccaccgccaccaccgccggacgctgtc
cctcgacaacagggactcggtggacctggccgagctggtgcccgcggtgggcgcccacccccgggccg
cctggagggcggcaggcccggcccccgggcatgaggactgcaatggcaggatgcccagcatcgccaaa
gacgtcttcaccaagatgggcgaccgcggggatcgcggggaggatgaggaggaaatcgactac

SSSRSSYYGPWGRSAAWASRRSSWNSLKHKPPSAEHESLLSAERGGGARVCEVAADEGPPRAAPLHTP
HAHHIHHGPHLAHRHRHHRRTLSLDNRDSVDLAELVPAVGAHPRAAWRAAGPAPGHEDCNGRMPSIAK
DVFTKMGDRGDRGEDEEEIDY

(SEQ ID NOs: 60 and 140) Exon 18 (constitutive)

accctgtgcttccgcgtccgcaagatgatcgacgtctataagcccgactggtgcgaggtccgcgaaga
ctggtctgtctacctcttctctcccgagaacag

TLCFRVRKMIDVYKPDWCEVREDWSVYLFSPENr

(SEQ ID NOs: 61 and 141) Exon 19 (constitutive)

gttccgggtcctgtgtcagaccattattgcccacaaactcttcgactacgtcgtcctggccttcatct
ttctcaactgcatcaccatcgccctggagcggcctcagatcgaggccggcagcacc

FRVLCQTIIAHKLFDYVVLAFIFLNCITIALERPQIEAGST

(SEQ ID NOs: 62 and 142) Exon 20 (constitutive)

gaacgcatctttctcaccgtgtccaactacatcttcacggccatcttcgtgggcgagatgacattgaa
g

ERIFLTVSNYIFTAIFVGEMTLK

(SEQ ID NOs: 63 and 143) Exon 21 (constitutive)

gtagtctcgctgggcctgtacttcggcgagcaggcgtacctacgcagcagctggaacgtgctggatgg
ctttcttgtcttcgtgtccatcatcgacatcgtggtgtccctggcctcagccgggggagccaagatct
tgggggtcctccgagtcttgcggctcctgcgcaccctacgccccctgcg

VVSLGLYFGEQAYLRSSWNVLDGFLVFVSIIDIVVSLASAGGAKILGVLRVLRLLRTLRPLr

(SEQ ID NOs: 64 and 144) Exon 22 (constitutive)

tgtcatcagccgggcgccgggcctgaagctggtggtggagacactcatctcctccctcaagcccatcg

gcaacatcgtgctcatctgctgtgccttcttcatcatctttggcatcctgggagtgcag

VISRAPGLKLVVETLISSLKPIGNIVLICCAFFIIFGILGVQ

(SEQ ID NOs: 65 and 145) Exon 23 (constitutive)

ctcttcaagggcaagttctaccactgtctgggcgtggacacccgcaacatcaccaaccgctcggactg

catggccgccaactaccgctgggtccatcacaaatacaacttcgacaacctgggccag

LFKGKFYHCLGVDTRNITNRSDCMAANYRWVHHKYNFDNLGQ

(SEQ ID NOs: 66 and 146) Exon 24 (constitutive)

gctctgatgtccctctttgtcctggcatccaaggatggttgggtgaacatcatgtacaatggactgga

tgctgttgctgtggaccagcag

ALMSLFVLASKDGWVNIMYNGLDAVAVDQQ

(SEQ ID NOs: 67 and 147) Exon 25 (constitutive)

cctgtgaccaaccacaacccctggatgctgctgtacttcatctccttcctgctcatcgtcagcttctt

tgtgctcaacatgtttgtgggtgtcgtggtggagaacttccacaagtgccggcagcaccaggaggctg

aagaggcacggcggcgtgaggagaagcggctgcggcgcctggagaagaagcgccgga

PVTNHNPWMLLYFISFLLIVSFFVLNMFVGVVVENFHKCRQHQEAEEARRREEKRLRRLEKKRR

(SEQ ID NOs: 68 and 148) Exon 26 (constitutive)

aggcccagcggctgccctactatgccacctattgtcacacccggctgctcatccactccatgtgcacc

agccactacctggacatcttcatcaccttcatcatctgcctcaacgtggtcaccatgtccctggagca

ctacaatcagcccacg

kAQRLPYYATYCHTRLLIHSMCTSHYLDIFITFIICLNVVTMSLEHYNQPT

(SEQ ID NOs: 69 and 149) Exon 27 (constitutive)

tccctggagacagccctcaagtactgcaactatatgttcaccactgtctttgtgctggaggctgtgct

gaagctggtggcatttggtctgaggcgcttcttcaaggaccg

SLETALKYCNYMFTTVFVLEAVLKLVAFGLRRFFKDr

(SEQ ID NOs: 70 and 150) Exon 28 (constitutive)

atggaaccagctggacctggccattgtgctactgtcagtcatgggcatcaccctggaggagatcgaga
tcaatgcggccctgcccatcaatcccaccatcatccgcatcatgagggttctgcgcattgcccgag

WNQLDLAIVLLSVMGITLEEIEINAALPINPTIIRIMRVLRIAR

(SEQ ID NOs: 71 and 151) Exon 29 (constitutive)

tgctgaagctgttgaagatggccacaggaatgcgggccctgctggacacggtggtgcaagctttgccc
cag

vLKLLKMATGMRALLDTVVQALPQ

(SEQ ID NOs: 72 and 152) Exon 30 (constitutive)

gtgggcaacctgggcctcctcttcatgctgctcttcttcatctatgctgctctcggggtggagctctt
tgggaagctgg

VGNLGLLFMLLFFIYAALGVELFGKL

(SEQ ID NOs: 73 and 153) Exon 31 (constitutive)

tctgcaacgacgagaacccgtgcgagggcatgagccggcatgccaccttcgagaacttcggcatggcc
ttcctcacactcttccaggtctccacgggtgacaactggaacgggatcatgaag

vCNDENPCEGMSRHATFENFGMAFLTLFQVSTGDNWNGIMK

(SEQ ID NOs: 74 and 154) Exon 32 (constitutive)

gacacgctgcgggactgcacccacgacgagcgcagctgcctgagcagcctgcagtttgtgtcgccgct
gtacttcgtgagcttcgtgctcaccgcgcagttcgtgctcatcaacgtggtggtggctgtgctcatga
agcacctggacgacagcaacaaggaggcgcaggaggacgccgagatggatgccgagctcgagctggag
atggcccatggcctgggccctggcccgaggctgcctaccggctccccgggcgcccctggccgagggcc
gggaggggcgggcggcgggggcgacaccgagggcggcttgtgccggcgctgctactcgcctgcccag

DTLRDCTHDERSCLSSLQFVSPLYFVSFVLTAQFVLINVVVAVLMKHLDDSNKEAQEDAEMDAELELE
MAHGLGPGPRLPTGSPGAPGRGPGGAGGGGDTEGGLCRRCYSPAQ

(SEQ ID NOs: 75 and 155) Exon 33A (variable)

gagaacctgtggctggacagcgtctctttaatcatcaag

ENLWLDSVSLIIK

(SEQ ID NOs: 76 and 156) Exon 33B (constitutive)

gactccttggaggggagctgaccatcatcgacaacctgtcgggctccatcttccaccactactcctc
gcctgccggctgcaagaagtgtcaccacgacaagcaagag

DSLEGELTIIDNLSGSIFHHYSSPAGCKKCHHDKQE

(SEQ ID NOs: 77 and 157) Exon 34 (constitutive)

gtgcagctggctgagacggaggccttctccctgaactcagacaggtcctcgtccatcctgctgggtga
cgacctgagtctcgaggaccccacagcctgcccacctggccgcaaagacagcaag

VQLAETEAFSLNSDRSSSILLGDDLSLEDPTACPPGRKDSK

(SEQ ID NOs: 78 and 158) Exon 35 (constitutive)

ggtgagctggacccacctgagcccatgcgtgtgggagacctgggcgaatgcttcttccccttgtcctc
tacggccgtctcgccggatccagagaacttcctgtgtgagatggaggagatcccattcaaccctgtcc
ggtcctggctgaaacatgacagcagtcaag

GELDPPEPMRVGDLGECFFPLSSTAVSPDPENFLCEMEEIPFNPVRSWLKHDSSQ

(SEQ ID NOs: 79 and 159) Exon 36A (constitutive)

caccccaagtcccttctccccggatgcctccagccctctcctgcccatgccagccgagttcttccac
cctgcagtgtctgccagccagaaaggcccagaaaagggcactggcactggaaccctccccaagattgc
gctgcagggctcctgggcatctctgcggtcaccaagggtcaactgtaccctcctccggcag

aPPSPFSPDASSPLLPMPAEFFHPAVSASQKGPEKGTGTGTLPKIALQGSWASLRSPRVNCTLLRQ

(SEQ ID NOs: 80 and 160) Exon 36B (mutually exclusive with Exon 37)

gtaccgacacctcccaggccctagagcactggtctgtgggcaaggggcaggatctaagccaggcct
ggaagtccaagggactgggaggggaaggacccaaccaaaggccgagggcaccaccgtgcaaggggg
tttgggaacgctggggtgacgctgagactggaggggggaggtggcactggggcggatggagtgggcg
gggctgggtcctggggacagcagagtgtggggaggaccccaaggcgggtctggaagaggcctgtga
tccctagcttgaggggagggggaggagaggaggaggagtactggaggttttgcagggtggcggggtg
ctggcagtggggaggacaccctgggtgctctgggtgggtgtgagtgggggcttgattactaggaat
ggaggtgggagggcgggtctggtggatgagaagcctcgggctgcagggtcccccgtactggattgg
ccagggccacagccctcctacccacgggcacacagaggtctgaagcactgagggctccgctgtggg
ggtggggaaatggggccgggccggctcccacagtgagtgcagttgattcactgggtgactgtctga
cccgtcacaccaggctgtgtgctctggcgggcaggacacaaactccctgcctgccgggctcactgt
ttagtgctgagagtgagctgcctgggtgcaggagggatgataaccaaaataaa
VPTPPRP-

(SEQ ID NOs: 81 and 161) Exon 37 (mutually exclusive with exon 36B)

gccaccgggagcgacacgtcgctggacgccagccccagcagctccgcgggcagcctgcagaccacgct
cgaggacagcctgaccctgagcgacagcccccggcgtgccctggggccgcccgcgcctgctccaggac
cccgggccggcctgtcccccgccgctcgccgccgcctgagcctgcgcggccggggcctcttcagcctg
cgggggctgcgggcgcatcagcgcagccacagcagcgggggctccaccagcccgggctgcacccacca

cgactccatggacccctcggacgaggagggccgcggtggcgcgggcggcgggggcgcgggcagcgagc
actcggagaccctcagcagcctctcgctcacctccctcttctgcccgccgcccccgccgccagccccc
ggcctcacgcccgccaggaagttcagcagcaccagcagcctggccgcccccggccgcccccacgccgc
cgccctggcccacggcctggcccggagcccctcgtgggccgcggaccgcagcaaggacccccccggcc
gggcaccgctgcccatgggcctgggcccctggcgcccccgccgcaaccgctcccccggagagctggag
ccgggagacgccgccagcaagaggaagagatgagggtcgcaggggcccccggccgcccaccgcccgcc
ccgtctcaccttctttacctcaggagccaggagcagacagcaatacttcgtccacacctgggatcgcg
cagggcccgcagggcacaggcgcccgacagccgggctgagcggagtctgggttagccaggcctgcgtg
gcccatggtggcccttccagtgcatatacatacatatatatatatatgcatatatatatatatatata
tatatatatgtgtatacacacacacatagacagacatatatatatatttatttttttactgagag
cttatgacttc
ATGSDTSLDASPSSSAGSLQTTLEDSLTLSDSPRRALGPPAPAPGPRAGLSPAARRRLSLRGRGLFSL
RGLRAHQRSHSSGGSTSPGCTHHDSMDPSDEEGRGGAGGGGAGSEHSETLSSLSLTSLFCPPPPPPAP
GLTPARKFSSTSSLAAPGRPHAAALAHGLARSPSWAADRSKDPPGRAPLPMGLGPLAPPPQPLPGELE
PGDAASKRKR-

RNA processing mechanisms

Figure 5 is a schematic diagram of the RNA processing leading to the 8 variants. The portion of the Figure above the scale bar represents the *CACNA1I* gene. The three sections of the gene involved in alternative processing are drawn to scale.

At the left, variable exon 9 (olive) is flanked by constitutive exons 8 (black) and 10 (purple). The black lines between exons represent introns.

In the middle, constitutive exon 32 is black. Exon 33 is divided into 2 parts, 39-nucleotide (nt) variable exon 33A (orange) and 108-nt constitutive exon 33B (blue).

At the right, exon 36 is divided into 2 parts, 197-nt constitutive exon 36A (black) and variable exon 36B (red), encoding seven aa before a stop codon. Constititive exon 37 (green) encodes 214 aa before a stop codon.

Exons 1 – 7, 11 –31 and 34 – 35 are not represented.

The blue and red lines and red arrow above and below the exons represent alternative RNA processing reactions.

Below the scale bar are representations of the 8 α_{1I} protein products. The portions of the protein derived from exons 1 – 7, 11 –31 and 34 – 35 are uncolored. Portions derived from the other exons are color-coded as in the gene map, above. Note that exon 36B encodes only 7 aa. The thin blue and red lines above the protein

products correspond to the lines around the gene map and represent the type of RNA processing reactions that resulted in the particular variant.

a. Alternative splicing of exon 9

Variants 1 – 4 result from the deletion of exon 9. In the blue reaction, splicing takes place between the donor 3′ to exon 8 and the acceptor 5′ to exon 10. Variants 5 – 8 result from RNAs subjected to the red reactions. In this case, two splicing reactions take place. The donor 3′ of exon 8 and the acceptor 5′ of exon 9 are joined as are the donor 3′ of exon 9 and the acceptor 5′ of exon 10. The portion encoded by exon 9 is retained.

b. Selection of the splice acceptor preceding exon 33A or 33B

Variants 1, 2, 5 and 6 result from the deletion of exon 33A. In the blue reaction, splicing takes place between the donor 3′ of exon 32 and the acceptor internal to exon 33. Variants 3, 4, 7 and 8 result from RNAs subjected to the red reaction. In this case, splicing takes place between the donor 3′ of exon 32 and the acceptor 5′ of exon 33. The portion encoded by exon 33A is retained.

c. Processing of the 3′ end

Variants 1, 3, 5 and 7 result from the deletion of exon 36B. In the blue reaction, splicing takes place between the donor internal to exon 36 and the acceptor 5′ of exon 37. Exon 37 encodes the final 214 aa of the protein in these variants. Variants 2, 4, 6 and 8 result from RNAs subjected to the red reaction. In this case, the RNA is cleaved and polyadenylated just 3′ of exon 36. In these variants, exon 36B encodes the final 7 aa of the protein.

Isolated and purified polypeptides or proteins, according to the present invention comprise at least about 10% by weight of a composition of proteins. Preferably the composition contains at least 25%, 50%, 75%, 85%, or 90% by weight of the particular polypeptide or protein. Any purification method can be applied, either to naturally expressing cells, such as neurons, or to cells which have been engineered to express a recombinant form of the polypeptide or protein. Purification methods known in the art which can be used without limitation include affinity chromatography, immunoprecipitation, immunoaffinity chromatography, molecular sieves, and ion exchange chromatography.

Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants, such as calcium channel function, are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequences shown in the SEQUENCE LISTING found at the end of the application. More preferably, the molecules are at least 98% or 99% identical. Percent identity is determined using the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* (1981) *2*:482-489.

Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer programs well known in the art, such as DNASTAR software. Preferably, amino acid changes in secreted protein variants are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting variant. Whether an amino acid change results in a functional calcium channel subunit protein or polypeptide can readily be determined by testing the altered protein or polypeptide in a functional assay.

Variants of the calcium channel subunit proteins disclosed herein include glycosylated forms, aggregative conjugates with other molecules, and covalent

conjugates with unrelated chemical moieties. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions, particularly exons, which do not affect functional activity of the proteins are also variants.

A subset of mutants, called muteins, is a group of polypeptides in which neutral amino acids, such as serines, are substituted for cysteine residues which do not participate in disulfide bonds. These mutants may be stable over a broader temperature range than native proteins or have other beneficial changes in physicochemical properties.

Any coding sequence can be used to generate a recombinant form of the protein which results in the proper amino acids being used. However, the natural human nucleic acid sequences are preferred. The coding sequence can be fused, for example, to expression control sequences, signal sequences, and/or to other coding sequences to form a fusion protein. All of the exons of a particular subunit can be used in such constructs. Alternatively one or more isolated exons can be used.

Nucleic acids which are isolated and purified are separated from the rest of the chromosome on which they reside in human cells. Preferably the particular nucleic acid is the predominant molecular species in a composition. More preferably the nucleic acid comprises at least 75%, 80%, 85%, 90%, or 95% of the molecular species (including only nucleic acids) in the composition.

Degenerate polynucleotide sequences which encode amino acid sequences of the proteins and variants, as well as homologous nucleotide sequences which are at least 65%, 75%, 85%, 90%, 95%, 98%, or 99% identical to the nucleotide sequences shown in the Sequence Listing are also polynucleotide molecules of the invention. Percent sequence identity is determined using computer programs which employ the Smith-Waterman algorithm, such as the MPSRCH program (Oxford Molecular), using an affine gap search with the following parameters: a gap open penalty of 12 and a gap extension penalty of 1.

Typically, homologous polynucleotide sequences can be confirmed by hybridization under stringent conditions, as is known in the art. For example, using

the following wash conditions--2 x SSC (0.3 M NaCl, 0.03 M sodium citrate, pH 7.0), 0.1% SDS, room temperature twice, 30 minutes each; then 2 x SSC, 0.1% SDS, 50 °C once, 30 minutes; then 2 x SSC, room temperature twice, 10 minutes each--homologous sequences can be identified which contain at most about 25-30% basepair mismatches. More preferably, homologous nucleic acid strands contain 15-25% basepair mismatches, even more preferably 5-15% basepair mismatches.

The nucleic acid can be cloned into a vector, particularly an expression vector. Any suitable expression vector as is known in the art may be used without limitation. Host cells are preferably used which are human, although other host cells including yeast, bacteria, insect, plant and mammalian cells can be used. The cells can be selected for their desired properties. Typically these are selected for their interaction with a vector, or for a property which renders nucleic acids or proteins easily obtainable from the cells.

Host cells which express an α_1 subunit according to the present invention or an α_1 polypeptide can be used to test compounds or compositions for their possible beneficial effect for treating epilepsy. Thus, a test substance can be contacted with such a host cell and the calcium ion uptake by the cell can be measured. A test substance which blocks calcium ion uptake by the cell is identified as a candidate drug for treating or preventing epilepsy. Methods for measuring calcium uptake are known in the art, and any such method may be used for drug identification. See for example, Lee *et al.*, *J. Neuroscience 19:*1912-21, 1999.

The following examples are provided to demonstrate how the invention was made. However, the subject matter of the invention is not limited to any particular method of making the claimed polypeptides, proteins, vectors, and host cells.

EXAMPLES

Example 1

Analysis of sequence produced by the Human Chromosome 22 Sequencing Group at the Sanger Centre revealed putative exons of a T α_1 subunit gene in three overlapping clones of a human genomic DNA library mapping to 22q12.3-13.2: dJ1104E15 (AL022312), dJ206C7 (AL008716) and dJ172B20 (AL022319). **tblastn** alignment with the α_1G (AF027984) or α_1H (AF051946) amino-acid (aa) sequence

identified 26 exons; **FEX** analysis, another six; and inspection of upstream sequence, a candidate exon encoding the N-terminus. Potential polyadenylation signals were located with **POLYAH**. Putative exons were assembled into a provisional cDNA sequence and primers for polymerase chain reaction (PCR)-amplification of overlapping portions of the cDNA were designed with **OLIGO** (National Biosciences).

PCR screening of a multiple-tissue cDNA panel (Clontech #K14201) revealed brain as the most abundant cDNA source. Hence, human brain cDNA (Clontech #74001) served as template in subsequent PCRs. The predominant (and in some cases secondary) product of each PCR was recovered on a spin-column (Qiagen #28704) after agarose gel electrophoresis, eluted in water and submitted for sequencing. Exon boundaries were determined by comparison of the cDNA and genomic sequences; ambiguity was resolved by matching potential donors and acceptors to consensus sequences.

Fig. 1 shows 28 of the 49 overlapping PCR products (top) that contributed to the cDNA sequence. Also pictured are exon maps of the cDNA (middle) and the gene (bottom). *CACNA1I* consists of at least 37 exons distributed over at least 116,390 basepairs (bp). Most PCRs yielded a single product suggesting constitutive splicing of 33 exons (colored gray or black in the cDNA and genomic maps). Certain PCRs, however, yielded multiple products (interrupted black bars), indicative of alternative splicing. PCRs spanning the 105-nucleotide (nt) exon 9 (red), for example, yielded two products, (14 and +14; thus, exon 9 is a cassette exon subject to type A alternative splicing. Sequencing of PCR products spanning exon 33 revealed that exon 33 harbors an internal acceptor that leads to type C alternative splicing and deletion of 39 nt at the 5′ end of the exon defined as exon 33A (orange).

Sequence analysis suggested the possibility of alternative 3′ exons. Indeed, PCR-amplification of brain cDNA followed by sequencing showed two forms with substantially different 3′ termini. In the first form, both exon 36A and 36B (green) are part of the mature mRNA. Exon 37 (blue) is presumably lost as a result of polyadenylation and cleavage at a site 686 bp downstream of the stop codon in exon 36B. In the second form, splicing between an alternative donor internal to exon 36

and the acceptor 5′ of exon 37 leads to substitution of exon 36B with exon 37. The polyadenylation signal of exon 37 has not been identified.

Introns 2 – 8 and 11 – 35 are common U2type GTAG introns. The donors of introns 9 and 10 begin with the dinucleotide GC. Intron 1, like its counterparts in *CACNA1G*, *CACNA1H* (unpublished observations), and *CACNA1A*, is a rare U12type ATAC intron. Exon 1 includes at least 709 bp of 5′ untranslated region and the putative start codon.

Fig. 2 shows a schematic of the deduced protein product. Sequence alignment with other members of the α_1 subunit family suggests a transmembrane topology with four domains (D1 – D4), each consisting of six membrane-spanning segments, a pore loop and cytoplasmic and extracellular connecting loops. The domains are linked by interdomain loops (ID12, ID23, ID34), which, along with the amino- (N) and carboxyl- (C) termini, reside in the cytoplasm. Six of the 35 α_1I splice sites (black bars) are conserved in the other α_1 subunits studied to date, α_{1A}, α_{1C}, α_{1D}, α_{1F}, α_{1S}, α_{1G} and α_{1H} and another three are located within nine nucleotides in the multiple sequence alignment (purple bars). Seventeen of the splice sites (green bars) are in identical locations in the other T subunits, but are not conserved in non-T subunits. Only nine splice sites (pink bars) are unique to α_1I; these sites join exons that contribute to the cytoplasmic ID1-2, ID2-3 and C-terminus. As indicated by residue color-coding, α_{1I} is quite similar to the two other human T α_1 subunits in its membrane-spanning segments — 84% of residues are identical and 92% have similarity scores (4 (see legend). Likewise, the pore loops and ID34 are similar. Apart from islands of similarity, the large extracellular loop of D1, the N- and C-termini and ID12 and ID23 differ from their counterparts in α_{1G} and α_{1H}. Five potential *N*-glycosylation sites in putative extracellular portions of the protein and 28 potential phosphorylation sites in putative cytoplasmic portions were identified with PROSITE. Although some of the potential phosphorylation sites are conserved among the T α_1 subunits, the majority are unique to α_{1I}. Seventeen extracellular cysteines, including six conserved in all ten reported human α_1 subunits (black and

purple hooks) and nine conserved among T α_1 subunits (green hooks), may play a role in maintaining proper conformation of the extracellular portions of the protein.

Regions derived from portions of the RNA subject to alternative processing are highlighted with a blue background. The shortest predicted product (Δ9Δ33AΔ37) has 1,968 aa residues; the longest (Δ36B), 2,223 aa residues. The reported rat orthologue corresponds to the human Δ9Δ36B variant with a few differences. Exon 32 of the human gene lacks an 18-aa stretch of cysteines, glycines and prolines found in rat (arrow). In addition, 40 nt of exon 34 are deleted in the rat sequence. This leads to a frameshift and early termination of the rat aa sequence. In addition, the published rat sequence contains sequencing errors in exon 35.

T currents display heterogeneity of biophysical and pharmacological properties and subcellular localization. Identification of multiple T α_1 subunit genes reveals one likely source of heterogeneity. Indeed, heterologous expression experiments demonstrate biophysical differences among the isoforms. The molecular diversity generated by alternative splicing of T α_1 subunit genes has the potential to yield additional functional diversity. *CACNA1I* is subject to alternative splicing in at least two exons while *CACNA1G* undergoes alternative splicing in at least six (unpublished observations). Variation in channel phosphorylation and isoform-specific interactions with other proteins may also contribute to diversity. Knowledge of the α_{1I} aa sequence and its variants will allow explicit tests of these ideas.

EXAMPLE 2

The human chromosome 17 genomic DNA of clone hCIT.22_K_21 (AC004590, Whitehead Institute/MIT Center for Genome Research) appeared to include most or all of *CACNA1G*, a gene encoding the T Ca^{2+} channel α_{1G} subunit. Thirty-four probable exons were identified by **blastn** alignment with the rat α_{1G} cDNA sequence (AF027984). Four potential polyadenylation signals were located by **blastn** alignment with sequences (R40146, R43876, R43935, R46109) derived from the 3′ end of infant brain cDNA clones. A provisional cDNA sequence was assembled and primers for polymerase chain reaction (PCR)-amplification of overlapping portions of human brain cDNA (Clontech #74001) were designed with **OLIGO** (National Biosciences).

PCR products were fractionated by agarose-gel electrophoresis. When adequately resolved, individual products were cut from the gel, recovered on a spin-column (Qiagen #28704), eluted in water and submitted for sequencing. When resolution was incomplete, DNA was recovered from the gel for cloning into pCRΔ2.1-TOPO (Invitrogen #K4500-01). Insert DNA was PCR-amplified from overnight cultures of white colonies, purified by agarose-gel electrophoresis and submitted for sequencing. Exon boundaries were determined by comparison of the cDNA and genomic sequences; ambiguity was resolved by matching potential donors and acceptors to consensus sequences. All reported splice variants were observed in at least two independent PCRs.

Fig. 3 shows 25 of the 83 overlapping PCR products (top, black bars) that contributed to the cDNA sequence (AF134985, AF134986). Also pictured are exon maps of the cDNA (middle) and the gene (bottom). *CACNA1G* consists of at least 38 exons distributed over at least 66,490 basepairs (bp). Thirty-four exons have conterparts in the rat cDNA sequence ; exons 14, 26, 34 and 35 are newly-identified. Most PCRs yielded a single product suggesting constitutive splicing of 32 exons (colored gray or black in the cDNA and genomic maps). Certain PCRs, however, yielded multiple products (interrupted black bars), indicative of alternative splicing. PCRs spanning the 69-nucleotide (nt) exon 14 (brown), for example, yielded two products, Δ14 and +14; thus, exon 14 is a cassette exon subject to type A alternative splicing. PCRs spanning cassette exons 34 (144 nt) and 35 (135 nt) yielded three products (Δ34Δ35, +34Δ35 and +34+35); the Δ34+35 product was not detected. Sequencing of PCR products spanning exons 25 and 26 revealed that exon 25 harbors an internal donor that leads to type D alternative splicing and deletion of 21 nt at the 3′ end of the exon (defined as exon 25B, red); the 54-nt exon 26 (blue) is a cassette exon. Exons 25B and 26 appear to be mutually exclusive in that only Δ25B+26 and +25BΔ26 variants were detected. Sequence data also demonstrated that a 237-nt, protein-coding portion of exon 38 (defined as exon 38B, green) could be excised as an intron (type E alternative splicing). Additional evidence for alternative processing of the human α_{1G} RNA comes from four clones of a normalized, oligo(dT)-primed infant brain cDNA library. Sequence derived from

these clones (red bars), suggests two polyadenylation sites: an upstream site 321 nt 3′ to the stop codon and a downstream site 719 nt 3′ to the stop codon. Cleavage at the upstream site would delete 398 nt of the mRNA, defined as exon 38D (purple). Exon 1 includes at least 432 bp of 5′ untranslated region and the putative start codon. Introns 2 – 37 are common U2type GTAG introns. Intron 1, like its counterparts in *CACNA1H* (unpublished observations), *CACNA1I* (submitted), and *CACNA1A*, is a rare U12type ATAC intron.

Fig. 4 shows a schematic of the deduced protein products encoded by *CACNA1G*. Like other members of the α_1 subunit family, α_{1G} has a proposed transmembrane topology with four domains (D1 – D4), each consisting of six membrane-spanning segments, a pore loop and cytoplasmic and extracellular connecting loops. The domains are linked by interdomain loops (ID12, ID23, ID34), which, along with the amino- (N) and carboxyl- (C) termini, reside in the cytoplasm. Regions derived from portions of the RNA subject to alternative splicing are highlighted with a blue background, with mutually-exclusive exons 25B and 26 placed side-by-side. The shortest predicted product (Δ14+25BΔ26Δ34Δ35Δ38B) has 2,171 amino-acid (aa) residues; the longest (+14Δ25B+26+34+35+38B), 2,377 aa residues. The reported rat α_{1G} aa sequence corresponds to the human (14+25BΔ26Δ34Δ35+38B splice variant and is 93% identical. Additional features of the α_{1G} protein product including residue similarity to the other T α_1 subunits, comparison of splice sites and sites of potential post-translational modification are shown in Fig. 2 and described in the legend.

Six *CACNA1G* exons undergo alternative splicing, leading to a possible 64 splice variants. Analysis of full-length PCR products is underway to determine relative splice-variant abundance. Of note, all potential variants maintain the open reading frame, leave the transmembrane topology intact and, hence, could be translated into plausible protein products. Individual α_{1G} isoforms may play distinct cellular roles by virtue of differences in biophysical behavior, protein-protein interactions, second-messenger-dependent regulation or other isoform-specific properties.

Claims

Claims:

1. An isolated and purified α_{1G} subunit of human brain T calcium channel selected from splice variants 1-64 as shown in Table 1.

2. An isolated and purified nucleic acid encoding the α_{1G} subunit of claim 1.

3. The isolated and purified nucleic acid of claim 2 which comprises a human coding sequence as described in Table 1.

4. An isolated and purified polypeptide which comprises a translated exon selected from the group consisting of 1-38D as shown in Table 2.

5. An isolated and purified nucleic acid which comprises an exon selected from the group consisting of 1-38D as shown in Table 2.

6. An isolated and purified α_{1I} subunit of human brain T calcium channel selected from splice variants 1-8 as shown in Table 3.

7. An isolated and purified nucleic acid encoding the α_{1I} subunit of claim 6.

8. The isolated and purified nucleic acid of claim 7 which comprises a human coding sequence as described in Table 3.

9. An isolated and purified polypeptide which comprises a translated exon selected from the group consisting of 1-37 as shown in Table 4.

10. An isolated and purified nucleic acid which comprises an exon selected from the group consisting of 1-37 as shown in Table 4.

11. An expression vector comprising the nucleic acid of claim 2.

12. An expression vector comprising the nucleic acid of claim 3.

13. An expression vector comprising the nucleic acid of claim 7.

14. An expression vector comprising the nucleic acid of claim 8.

15. A host cell comprising an expression vector according to claim 11.

16. A host cell comprising an expression vector according to claim 12.

17. A host cell comprising an expression vector according to claim 13.

18. A host cell comprising an expression vector according to claim 14.

19. A method to identify candidate drugs for treating epilepsy, comprising the steps of:

contacting a cell according to claim 15 with a test substance;

measuring uptake by the cell of calcium ions, wherein a test substance which inhibits the uptake by the cell of calcium ions is identified as a candidate drug for treating epilepsy.

20. A method to identify candidate drugs for treating epilepsy, comprising the steps of:

contacting a cell according to claim 16 with a test substance;

measuring uptake by the cell of calcium ions, wherein a test substance which inhibits the uptake by the cell of calcium ions is identified as a candidate drug for treating epilepsy.

21. A method to identify candidate drugs for treating epilepsy, comprising the steps of:

contacting a cell according to claim 17 with a test substance;

measuring uptake by the cell of calcium ions, wherein a test substance which inhibits the uptake by the cell of calcium ions is identified as a candidate drug for treating epilepsy.

22. A method to identify candidate drugs for treating epilepsy, comprising the steps of:

contacting a cell according to claim 18 with a test substance;

measuring uptake by the cell of calcium ions, wherein a test substance which inhibits the uptake by the cell of calcium ions is identified as a candidate drug for treating epilepsy.

FIG. 1

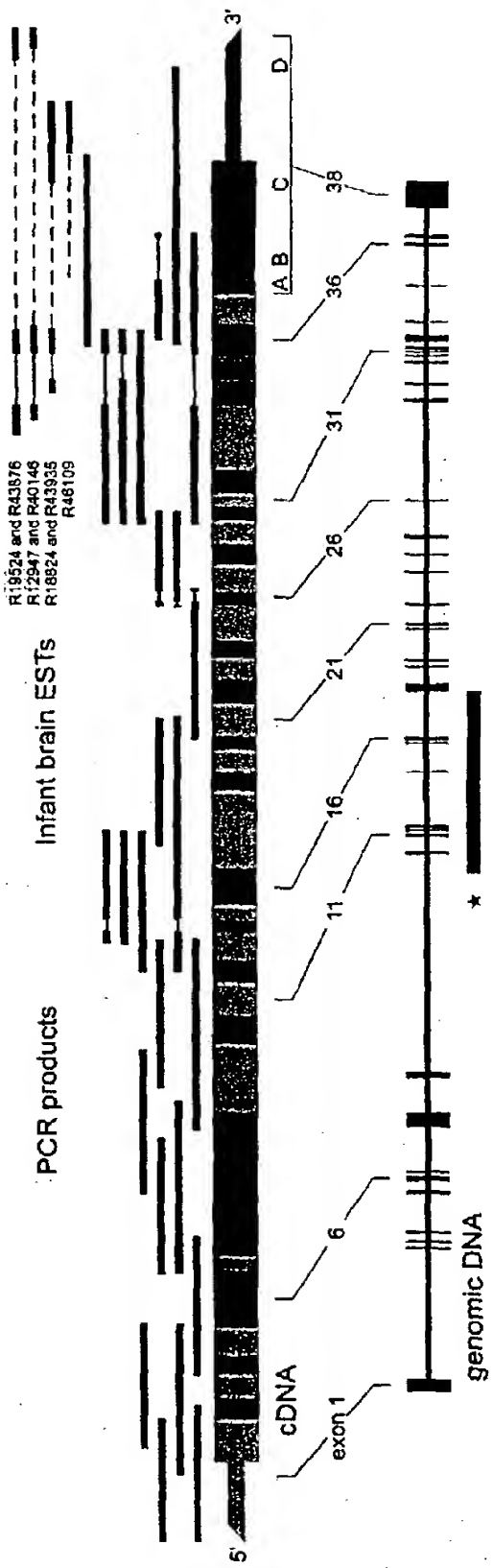
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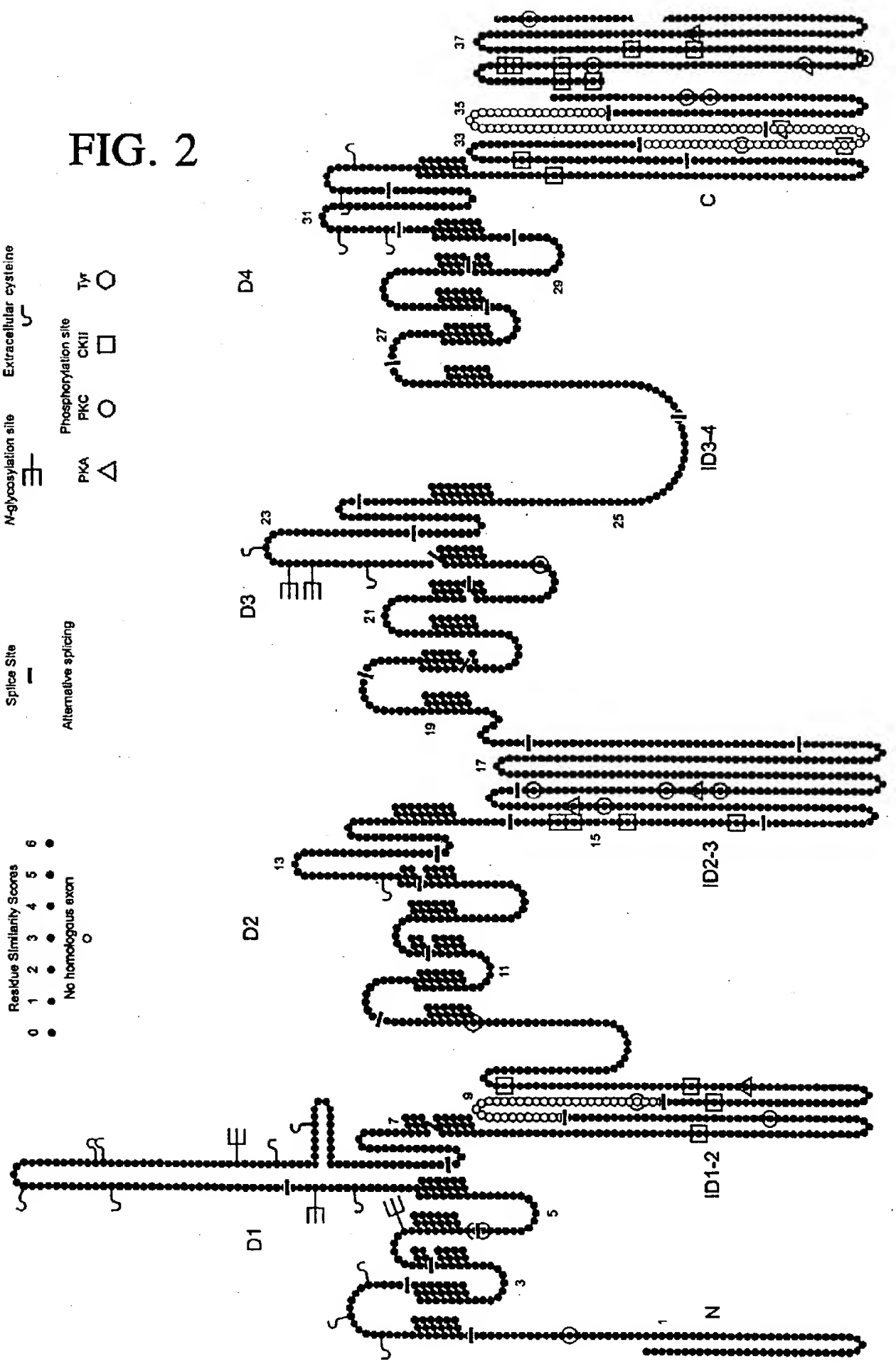
FIG. 2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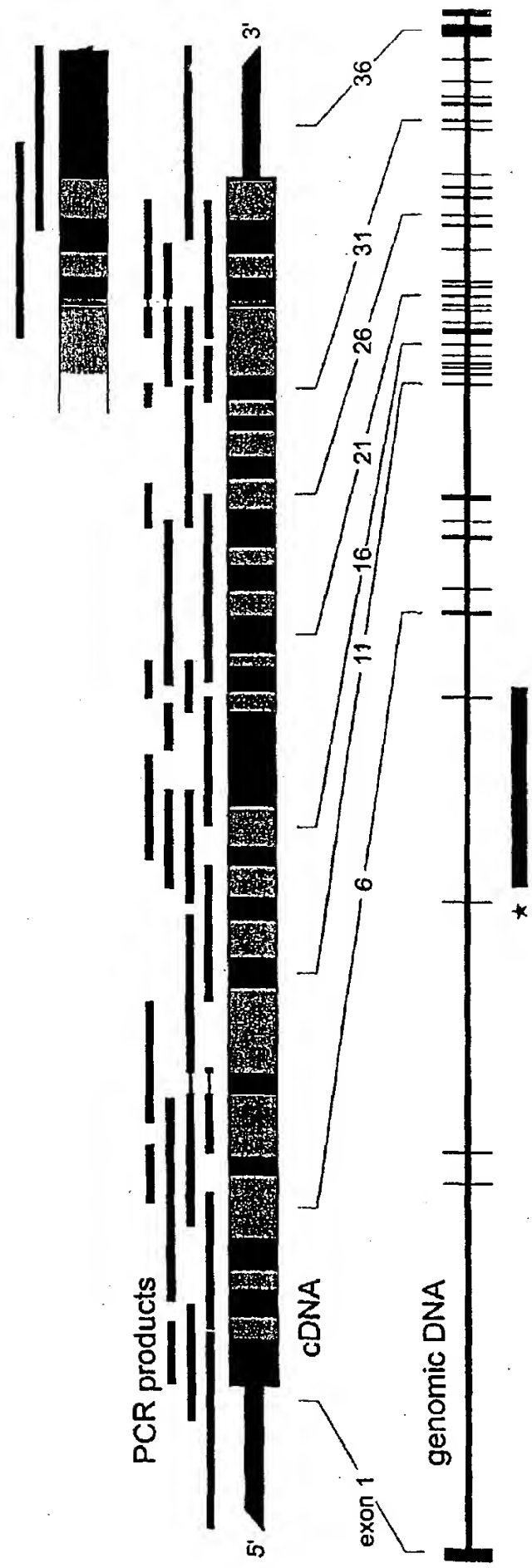

FIG. 3

FIG. 4

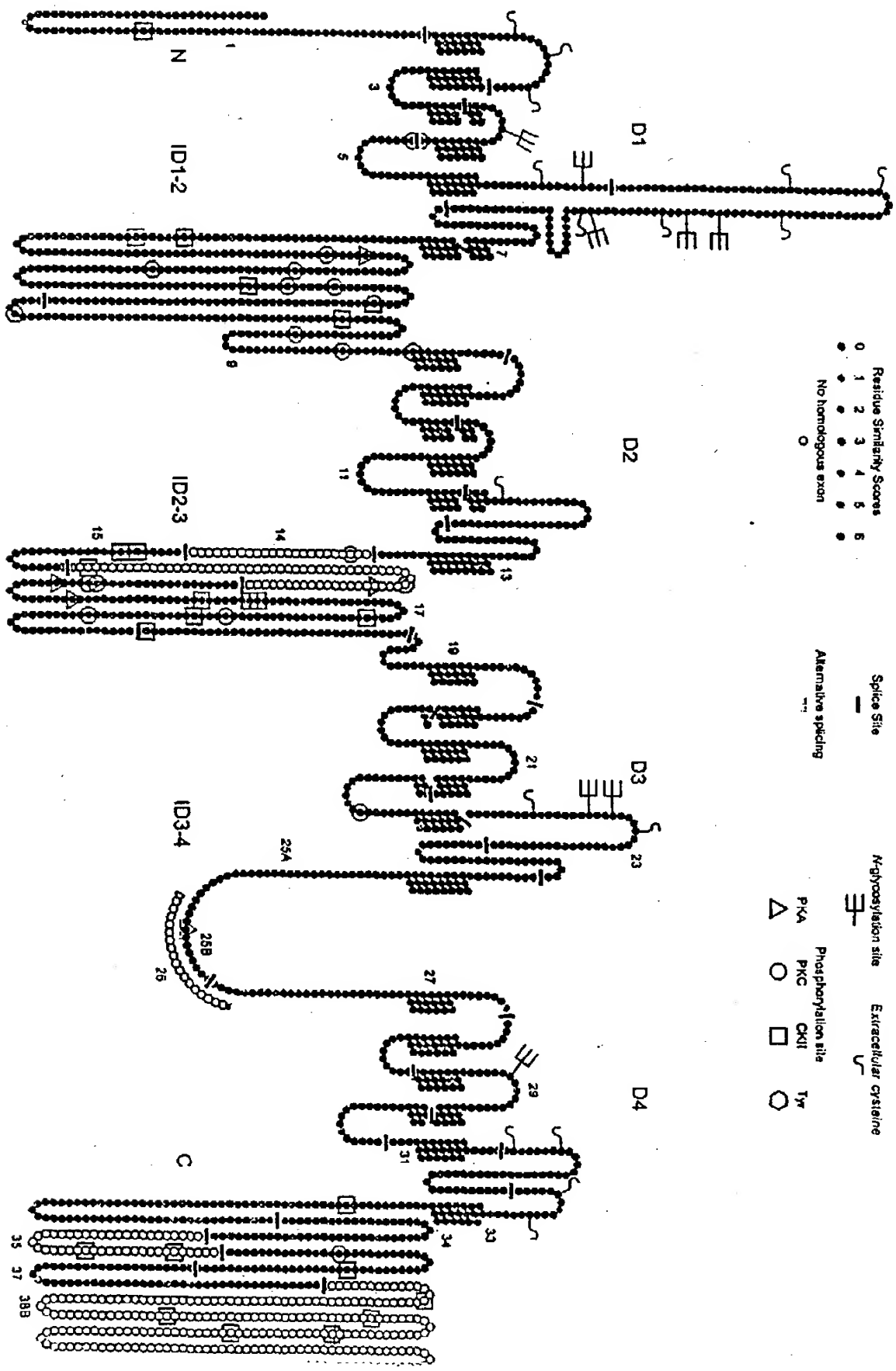
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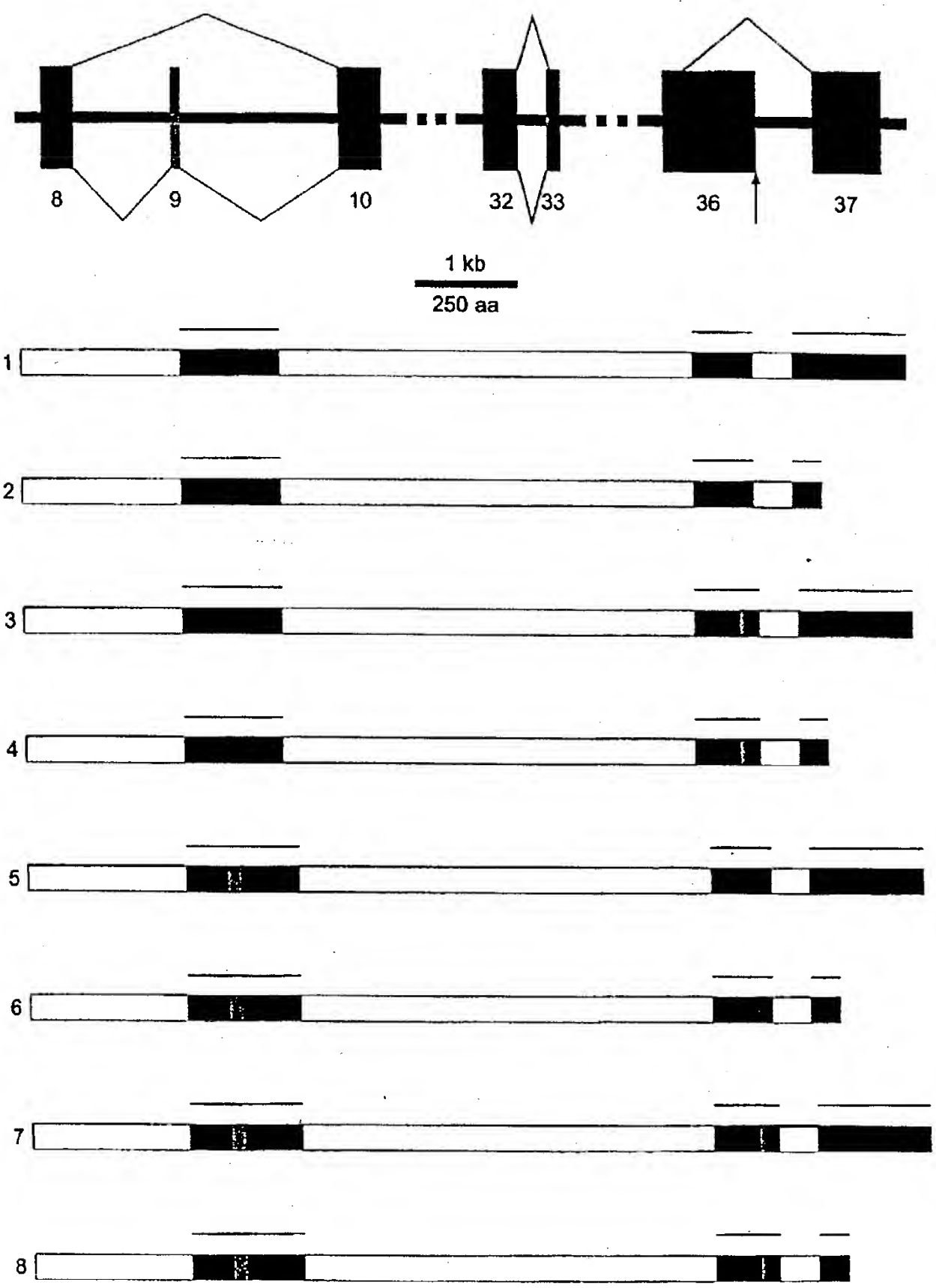
FIG. 5



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<210> 32
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gagctctttg gagacctgg 79

<210> 33
<211> 122
<212> DNA
<213> Homo sapiens

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<210> 34
<211> 354
<212> DNA
<213> Homo sapiens

<400> 34
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ctgatgaagc acctggagga gagcaacaag gaggccaagg aggaggccga gctagaggct 180
gagctggagc tggagatgaa gaccctcagc ccccagcccc actcgccact gggcagcccc 240
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<210> 35
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<212> DNA
<213> Homo sapiens

<400> 35
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agcctgggag gctccgaccc acag 144

<210> 36
<211> 135
<212> DNA
<213> Homo sapiens

<400> 36
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gccctggaga gcaat 135

<210> 37
<211> 169
<212> DNA
<213> Homo sapiens

<400> 37
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<210> 38
<211> 170
<212> DNA
<213> Homo sapiens

<400> 38
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tgcccccacc aggacgctcc cctttggctc agaggccact caggcgccag 170

<210> 39
<211> 66
<212> DNA
<213> Homo sapiens

<400> 39
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gcagag 66

<210> 40
<211> 237
<212> DNA
<213> Homo sapiens

<400> 40
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caggcacagc agcactcccg cagccacagc aagatctcca agcacatgac cccgccagcc 120
ccttgcccag gcccagaacc caactggggc aagggccctc cagagaccag aagcagctta 180
gagttggaca cggagctgag ctggatttca ggagacctcc tgccccctgg cggccag 237

<210> 41
<211> 753
<212> DNA
<213> Homo sapiens

<400> 41
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<210> 42
<211> 402
<212> DNA
<213> Homo sapiens

<400> 42
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tctagttata ttcccctcttc ttgcaaagca caagctggga ccgcgagcac attgcagccc 180
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atctatatat atataaaata aagtaatttt cctaaataaa aa 402

<210> 43
<211> 236
<212> DNA
<213> Homo sapiens

<400> 43
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gtcaccacgg agcagcccgg accccggagc cccccatcct ccccgccagg cctggaggag 120
cctctggatg gagctgatcc tcatgtccca cacccagacc tggcgcctat tgccttcttc 180
tgcctgcgac agaccaccag ccccccggaac tggtgcatca agatggtgtg caaccc 236

<210> 44
<211> 112
<212> DNA
<213> Homo sapiens

<400> 44
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ccagccgtgc gacgacatgg actgcctgtc cgaccgctgc aagatcctgc ag 112

<210> 45
<211> 134
<212> DNA
<213> Homo sapiens

<400> 45
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ctggggattt ttggcaagaa gtgctacctc ggggacacat ggaaccgcct ggatttcttc 120
atcgtcatgg cagg 134

<210> 46

<211> 98
<212> DNA
<213> Homo sapiens

<400> 46
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cgtcctgagg cccctcaaag ccatcaaccg cgtgccca 98

<210> 47
<211> 160
<212> DNA
<213> Homo sapiens

<400> 47
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tgctctgctt ctttgtcttc ttcatctttg gcatcatagg tgtgcagctc tgggcgggcc 120
tgctgcgtaa ccgctgcttc ctggaggaga acttcaccat 160

<210> 48
<211> 316
<212> DNA
<213> Homo sapiens

<400> 48
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catctgctcc ctgtcgggcg acaatgggat aatgggctgc catgagatcc ccccgctcaa 120
ggagcagggc cgtgagtgct gcctgtccaa ggacgacgtc tacgactttg gggcggggcg 180
ccaggacctc aatgccagcg gcctctgtgt caactggaac cgttactaca atgtgtgccg 240
cacgggcagc gccaaccccc acaagggtgc catcaacttt gacaacatcg gttatgcttg 300
gattgtcatc ttccag 316

<210> 49
<211> 93
<212> DNA
<213> Homo sapiens

<400> 49
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tacaacttca tctacttcat cctgcttatc ata 93

<210> 50
<211> 313
<212> DNA
<213> Homo sapiens

<400> 50
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acggtggcca gctacgccga gcctggcgac tgctacgagg agatcttcca gtatgtctgc 180
cacatcctgc gcaaggccaa gcgccgcgcc ctgggcctct accaggccct gcagagccgg 240
cgccaggccc tgggcccgga ggccccggcc cccgccaaac ctgggcccca cgccaaggag 300
ccccggcact acc 313

<210> 51
<211> 105

<212> DNA
<213> Homo sapiens

<400> 51
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ctttgcatgg gcctgcctcc cctggaaatg atcactcggg aagag 105

<210> 52
<211> 425
<212> DNA
<213> Homo sapiens

<400> 52
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ccgccacgct ggcttccgat cccgccagct gcccttgctg ccagcatgag gacggccggc 120
ggccctcggg cctgggcagc accgactcgg gccaggaggg ctcgggctcc gggagctccg 180
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cagaactggg gaaggaggag gaggaggagg agcaggcgga tggggcggtc tggctgtgcg 300
gggatgtgtg gcgggagacg cgagccaagc tgcgcggcat cgtggacagc aagtacttca 360
accggggcat catgatggcc atcctggtca acaccgtcag catgggcatc gagcaccacg 420
agcag 425

<210> 53
<211> 152
<212> DNA
<213> Homo sapiens

<400> 53
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ctggagatga tcctgaagct ggctgcattt gggctcttcg actacctgcg taacccctac 120
aacatcttcg acagcatcat tgtcatcatc ag 152

<210> 54
<211> 186
<212> DNA
<213> Homo sapiens

<400> 54
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gctgcgcgtg ctgaaactgg tgcgcttcat gcctgccctg cggcgccagc tcgtggtgct 120
catgaagacc atggacaacg tggccacctt ctgcatgctg ctcatgctct tcatcttcat 180
cttcag 186

<210> 55
<211> 118
<212> DNA
<213> Homo sapiens

<400> 55
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ggtgcccgac aggaagaact tcgactcccc gctgtgggcc atcgtcactg tgttccag 118

<210> 56
<211> 156
<212> DNA

<213> Homo sapiens

<400> 56
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tgggcctccc tctactttgt cgccctcatg accttcggca actatgtgct cttcaacctg 120
ctggtggcca tcctggtgga gggcttccag gcggag 156

<210> 57
<211> 94
<212> DNA
<213> Homo sapiens

<400> 57
ggtgacgcca atcgctccta ctcggacgag gaccagagct catccaacat agaagagttt 60
gataagctcc aggaaggcct ggacagcagc ggag 94

<210> 58
<211> 203
<212> DNA
<213> Homo sapiens

<400> 58
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tgggtgggca cctaggtcct gctggggctg cgggacctgc cccccgactc tcactgcagc 120
cggaccccat gctggtggcc ctgggctccc gaaagagcag tgtcatgtct ctagggagga 180
tgagctatga ccagcgctcc ctg 203

<210> 59
<211> 471
<212> DNA
<213> Homo sapiens

<400> 59
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tctgcggagc gcggcggcgg cgcccgggtc tgcgaggttg ccgcggacga ggggccgccg 180
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caccgccacc gccaccaccg ccggacgctg tccctcgaca acagggactc ggtggacctg 300
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gcccccgggc atgaggactg caatggcagg atgcccagca tcgccaaaga cgtcttcacc 420
aagatgggcg accgcgggga tcgcggggag gatgaggagg aaatcgacta c 471

<210> 60
<211> 101
<212> DNA
<213> Homo sapiens

<400> 60
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cgcgaagact ggtctgtcta cctcttctct cccgagaaca g 101

<210> 61
<211> 124
<212> DNA
<213> Homo sapiens

<400> 61
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cttcatcttt ctcaactgca tcaccatcgc cctggagcgg cctcagatcg aggccggcag 120
cacc 124

<210> 62
<211> 69
<212> DNA
<213> Homo sapiens

<400> 62
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acattgaag 69

<210> 63
<211> 185
<212> DNA
<213> Homo sapiens

<400> 63
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ctggatggct ttcttgtctt cgtgtccatc atcgacatcg tggtgtccct ggcctcagcc 120
gggggagcca agatcttggg ggtcctccga gtcttgcggc tcctgcgcac cctacgcccc 180
ctgcg 185

<210> 64
<211> 127
<212> DNA
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<400> 64
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gcccatcggc aacatcgtgc tcatctgctg tgccttcttc atcatctttg gcatcctggg 120
agtgcag 127

<210> 65
<211> 126
<212> DNA
<213> Homo sapiens

<400> 65
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tcggactgca tggccgccaa ctaccgctgg gtccatcaca aatacaactt cgacaacctg 120
ggccag 126

<210> 66
<211> 90
<212> DNA
<213> Homo sapiens

<400> 66
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ggactggatg ctgttgctgt ggaccagcag 90

<210> 67

<211> 193
<212> DNA
<213> Homo sapiens

<400> 67
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cagcaccagg aggctgaaga ggcacggcgg cgtgaggaga agcggctgcg gcgcctggag 180
aagaagcgcc gga 193

<210> 68
<211> 152
<212> DNA
<213> Homo sapiens

<400> 68
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ccatgtccct ggagcactac aatcagccca cg 152

<210> 69
<211> 110
<212> DNA
<213> Homo sapiens

<400> 69
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gctgtgctga agctggtggc atttggtctg aggcgcttct tcaaggaccg 110

<210> 70
<211> 134
<212> DNA
<213> Homo sapiens

<400> 70
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gatcgagatc aatgcggccc tgcccatcaa tcccaccatc atccgcatca tgagggttct 120
gcgcattgcc cgag 134

<210> 71
<211> 71
<212> DNA
<213> Homo sapiens

<400> 71
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ctttgcccca g 71

<210> 72
<211> 79
<212> DNA
<213> Homo sapiens

<400> 72
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gagctctttg ggaagctgg 79

<210> 73
<211> 122
<212> DNA
<213> Homo sapiens

<400> 73
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ag 122

<210> 74
<211> 339
<212> DNA
<213> Homo sapiens

<400> 74
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<210> 75
<211> 39
<212> DNA
<213> Homo sapiens

<400> 75
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<210> 76
<211> 108
<212> DNA
<213> Homo sapiens

<400> 76
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<210> 77
<211> 123
<212> DNA
<213> Homo sapiens

<400> 77
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aag 123

<210> 78
<211> 166
<212> DNA

<213> Homo sapiens

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ccattcaacc ctgtccggtc ctggctgaaa catgacagca gtcaag 166

<210> 79
<211> 197
<212> DNA
<213> Homo sapiens

<400> 79
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ccctccccaa gattgcgctg cagggctcct gggcatctct gcggtcacca agggtcaact 180
gtaccctcct ccggcag 197

<210> 80
<211> 713
<212> DNA
<213> Homo sapiens

<400> 80
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<210> 81
<211> 963
<212> DNA
<213> Homo sapiens

<400> 81
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caatacttcg tccacacctg ggatcgcgca gggcccgcag ggcacaggcg cccgacagcc 780
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tatacataca tatatatata tatatgcata tatatatata tatatatata tatgtgtata 900
cacacacaca tagacagaca tatatatata tatttatttt ttttactgag agcttatgac 960
ttc 963

<210> 82
<211> 81
<212> PRT
<213> Homo sapiens

<400> 82
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Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro
20 25 30
Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
35 40 45
Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
50 55 60
Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
65 70 75 80
Pro

<210> 83
<211> 37
<212> PRT
<213> Homo sapiens

<400> 83
Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr
1 5 10 15
Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln Arg
20 25 30
Cys Arg Ile Leu Gln
35

<210> 84
<211> 45
<212> PRT
<213> Homo sapiens

<400> 84
Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe Ala Val Glu Met Val Val
1 5 10 15
Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr Leu Gly Asp
20 25 30
Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Ile Ala Gly
35 40 45

<210> 85
<211> 32
<212> PRT
<213> Homo sapiens

<400> 85
Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe Ser Ala Val
1 5 10 15
Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn Arg Val Pro
20 25 30

<210> 86
<211> 54
<212> PRT
<213> Homo sapiens

<400> 86
Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu Pro Met Leu
1 5 10 15
Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly Ile
20 25 30
Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu
35 40 45
Pro Glu Asn Phe Ser Leu
50

<210> 87
<211> 100
<212> PRT
<213> Homo sapiens

<400> 87
Pro Leu Ser Val Asp Leu Glu Arg Tyr Tyr Gln Thr Glu Asn Glu Asp
1 5 10 15
Glu Ser Pro Phe Ile Cys Ser Gln Pro Arg Glu Asn Gly Met Arg Ser
20 25 30
Cys Arg Ser Val Pro Thr Leu Arg Gly Asp Gly Gly Gly Gly Pro Pro
35 40 45
Cys Gly Leu Asp Tyr Glu Ala Tyr Asn Ser Ser Ser Asn Thr Thr Cys
50 55 60
Val Asn Trp Asn Gln Tyr Tyr Thr Asn Cys Ser Ala Gly Glu His Asn
65 70 75 80
Pro Phe Lys Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile
85 90 95
Ala Ile Phe Gln
100

<210> 88
<211> 31
<212> PRT
<213> Homo sapiens

<400> 88
Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp
1 5 10 15
Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
20 25 30

<210> 89
<211> 261

<212> PRT
<213> Homo sapiens

<400> 89

```
Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr
 1               5                  10                  15
Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln
            20                  25                  30
Arg Val Arg Phe Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu
        35                  40                  45
Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu
    50                  55                  60
Arg Lys Ala Ala Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val
65                  70                  75                  80
Arg Val Gly Leu Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr
                85                  90                  95
Gln Pro Ser Ser Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His
            100                 105                 110
His Leu Val His His His His His His His His His Tyr His Leu Gly
        115                 120                 125
Asn Gly Thr Leu Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg
    130                 135                 140
Asp Ala Asn Gly Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro
145                 150                 155                 160
Ala Leu Ser Gly Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe
                165                 170                 175
Tyr His Ala Asp Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro
            180                 185                 190
Pro Arg Ser Pro Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys
        195                 200                 205
Val Tyr Pro Thr Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu
    210                 215                 220
Lys Ala Leu Val Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr
225                 230                 235                 240
Ser Leu Asn Ile Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu
                245                 250                 255
Glu Thr Gln Ser Thr
            260
```

<210> 90
<211> 126
<212> PRT
<213> Homo sapiens

<400> 90

```
Gly Ala Cys Gln Ser Ser Cys Lys Ile Ser Ser Pro Cys Leu Lys Ala
 1               5                  10                  15
Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg Ala
            20                  25                  30
Gly Ala Gly Glu Val Glu Leu Ala Asp Arg Glu Met Pro Asp Ser Asp
        35                  40                  45
Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp Leu
    50                  55                  60
Arg Asp Pro His Ser Arg Arg Gln Arg Ser Leu Gly Pro Asp Ala Glu
65                  70                  75                  80
```

```
Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr Phe Arg
                85                  90                  95
Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile Ala Ile
            100                 105                 110
Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln
        115                 120                 125
```

<210> 91
<211> 51
<212> PRT
<213> *Homo sapiens*

<400> 91

```
Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr
 1               5                  10                  15
Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro
            20                  25                  30
Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val
        35                  40                  45
Val Ile Ser
    50
```

<210> 92
<211> 62
<212> PRT
<213> Homo sapiens

<400> 92

```
Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser Val Leu Arg
 1               5                  10                  15
Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe Leu Pro Ala
            20                  25                  30
Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp Asn Val Ala
        35                  40                  45
Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser
    50                  55                  60
```

<210> 93
<211> 38
<212> PRT
<213> Homo sapiens

<400> 93

```
Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg Asp
 1               5                  10                  15
Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala
            20                  25                  30
Ile Val Thr Val Phe Gln
        35
```

<210> 94
<211> 52
<212> PRT
<213> Homo sapiens

<400> 94
Ile Leu Thr Gln Glu Asp Trp Asn Lys Val Leu Tyr Asn Gly Met Ala
1 5 10 15
Ser Thr Ser Ser Trp Ala Ala Leu Tyr Phe Ile Ala Leu Met Thr Phe
20 25 30
Gly Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val Glu Gly
35 40 45
Phe Gln Ala Glu
50

<210> 95
<211> 23
<212> PRT
<213> Homo sapiens

<400> 95
Glu Ile Ser Lys Arg Glu Asp Ala Ser Gly Gln Leu Ser Cys Ile Gln
1 5 10 15
Leu Pro Val Asp Ser Gln Gly
20

<210> 96
<211> 28
<212> PRT
<213> Homo sapiens

<400> 96
Gly Asp Ala Asn Lys Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser
1 5 10 15
Leu Asp Gly Asp Gly Asp Arg Lys Lys Cys Leu Ala
20 25

<210> 97
<211> 65
<212> PRT
<213> Homo sapiens

<400> 97
Leu Val Ser Leu Gly Glu His Pro Glu Leu Arg Lys Ser Leu Leu Pro
1 5 10 15
Pro Leu Ile Ile His Thr Ala Ala Thr Pro Met Ser Leu Pro Lys Ser
20 25 30
Thr Ser Thr Gly Leu Gly Glu Ala Leu Gly Pro Ala Ser Arg Arg Thr
35 40 45
Ser Ser Ser Gly Ser Ala Glu Pro Gly Ala Ala His Glu Met Lys Ser
50 55 60
Pro
65

<210> 98
<211> 144
<212> PRT
<213> Homo sapiens

<400> 98

```
Pro Ser Ala Arg Ser Ser Pro His Ser Pro Trp Ser Ala Ala Ser Ser
 1               5                  10                  15
Trp Thr Ser Arg Arg Ser Ser Arg Asn Ser Leu Gly Arg Ala Pro Ser
            20                  25                  30
Leu Lys Arg Arg Ser Pro Ser Gly Glu Arg Arg Ser Leu Leu Ser Gly
        35                  40                  45
Glu Gly Gln Glu Ser Gln Asp Glu Glu Glu Ser Ser Glu Glu Glu Arg
    50                  55                  60
Ala Ser Pro Ala Gly Ser Asp His Arg His Arg Gly Ser Leu Glu Arg
65                  70                  75                  80
Glu Ala Lys Ser Ser Phe Asp Leu Pro Asp Thr Leu Gln Val Pro Gly
                85                  90                  95
Leu His Arg Thr Ala Ser Gly Arg Gly Ser Ala Ser Glu His Gln Asp
            100                 105                 110
Cys Asn Gly Lys Ser Ala Ser Gly Arg Leu Ala Arg Ala Leu Arg Pro
        115                 120                 125
Asp Asp Pro Pro Leu Asp Gly Asp Asp Ala Asp Asp Glu Gly Asn Leu
    130                 135                 140
```

<210> 99
<211> 34
<212> PRT
<213> Homo sapiens

<400> 99

```
Ser Lys Gly Glu Arg Val Arg Ala Trp Ile Arg Ala Arg Leu Pro Ala
 1               5                  10                  15
Cys Cys Leu Glu Arg Asp Ser Trp Ser Ala Tyr Ile Phe Pro Pro Gln
            20                  25                  30
Ser Arg
```

<210> 100
<211> 41
<212> PRT
<213> Homo sapiens

<400> 100

```
Phe Arg Leu Leu Cys His Arg Ile Ile Thr His Lys Met Phe Asp His
 1               5                  10                  15
Val Val Leu Val Ile Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu
            20                  25                  30
Arg Pro Lys Ile Asp Pro His Ser Ala
        35                  40
```

<210> 101
<211> 23
<212> PRT
<213> Homo sapiens

<400> 101

```
Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala Val Phe
 1               5                  10                  15
Leu Ala Glu Met Thr Val Lys
            20
```

<210> 102
<211> 62
<212> PRT
<213> Homo sapiens

<400> 102
Val Val Ala Leu Gly Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser
1 5 10 15
Ser Trp Asn Val Leu Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp
20 25 30
Ile Leu Val Ser Met Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met
35 40 45
Leu Arg Val Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg
50 55 60

<210> 103
<211> 42
<212> PRT
<213> Homo sapiens

<400> 103
Val Ile Ser Arg Ala Gln Gly Leu Lys Leu Val Val Glu Thr Leu Met
1 5 10 15
Ser Ser Leu Lys Pro Ile Gly Asn Ile Val Val Ile Cys Cys Ala Phe
20 25 30
Phe Ile Ile Phe Gly Ile Leu Gly Val Gln
35 40

<210> 104
<211> 42
<212> PRT
<213> Homo sapiens

<400> 104
Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp Thr Arg Asn
1 5 10 15
Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg Trp Val Arg
20 25 30
His Lys Tyr Asn Phe Asp Asn Leu Gly Gln
35 40

<210> 105
<211> 30
<212> PRT
<213> Homo sapiens

<400> 105
Ala Leu Met Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp
1 5 10 15
Ile Met Tyr Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln
20 25 30

<210> 106
<211> 64
<212> PRT

<213> Homo sapiens

<400> 106
Pro Ile Met Asn His Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe
1 5 10 15
Leu Leu Ile Val Ala Phe Phe Val Leu Asn Met Phe Val Gly Val Val
20 25 30
Val Glu Asn Phe His Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala
35 40 45
Arg Arg Arg Glu Glu Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg
50 55 60

<210> 107
<211> 7
<212> PRT
<213> Homo sapiens

<400> 107
Ser Lys Glu Lys Gln Met Ala
1 5

<210> 108
<211> 18
<212> PRT
<213> Homo sapiens

<400> 108
Asn Leu Met Leu Asp Asp Val Ile Ala Ser Gly Ser Ser Ala Ser Ala
1 5 10 15
Ala Ser

<210> 109
<211> 51
<212> PRT
<213> Homo sapiens

<400> 109
Glu Ala Gln Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu
1 5 10 15
Leu Val His His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr
20 25 30
Gly Val Ile Gly Leu Asn Val Val Thr Met Ala Met Glu His Tyr Gln
35 40 45
Gln Pro Gln
50

<210> 110
<211> 37
<212> PRT
<213> Homo sapiens

<400> 110
Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile
1 5 10 15

Phe Val Leu Glu Ser Val Phe Lys Leu Val Ala Phe Gly Phe Arg Arg
20 25 30
Phe Phe Gln Asp Arg
35

<210> 111
<211> 44
<212> PRT
<213> Homo sapiens

<400> 111
Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser Ile Met Gly Ile
1 5 10 15
Thr Leu Glu Glu Ile Glu Val Asn Ala Ser Leu Pro Ile Asn Pro Thr
20 25 30
Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg
35 40

<210> 112
<211> 24
<212> PRT
<213> Homo sapiens

<400> 112
Val Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu Asp
1 5 10 15
Thr Val Met Gln Ala Leu Pro Gln
20

<210> 113
<211> 26
<212> PRT
<213> Homo sapiens

<400> 113
Val Gly Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala
1 5 10 15
Ala Leu Gly Val Glu Leu Phe Gly Asp Leu
20 25

<210> 114
<211> 41
<212> PRT
<213> Homo sapiens

<400> 114
Glu Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala Thr
1 5 10 15
Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser Thr
20 25 30
Gly Asp Asn Trp Asn Gly Ile Met Lys
35 40

<210> 115
<211> 118

<212> PRT
<213> Homo sapiens

<400> 115
Asp Thr Leu Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val
1 5 10 15
Ile Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe Val
20 25 30
Leu Val Asn Val Val Ile Ala Val Leu Met Lys His Leu Glu Glu Ser
35 40 45
Asn Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu
50 55 60
Glu Met Lys Thr Leu Ser Pro Gln Pro His Ser Pro Leu Gly Ser Pro
65 70 75 80
Phe Leu Trp Pro Gly Val Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys
85 90 95
Pro Gly Ala Leu His Pro Ala Ala His Ala Arg Ser Ala Ser His Phe
100 105 110
Ser Leu Glu His Pro Thr
115

<210> 116
<211> 48
<212> PRT
<213> Homo sapiens

<400> 116
Asp Arg Gln Leu Phe Asp Thr Ile Ser Leu Leu Ile Gln Gly Ser Leu
1 5 10 15
Glu Trp Glu Leu Lys Leu Met Asp Glu Leu Ala Gly Pro Gly Gly Gln
20 25 30
Pro Ser Ala Phe Pro Ser Ala Pro Ser Leu Gly Gly Ser Asp Pro Gln
35 40 45

<210> 117
<211> 45
<212> PRT
<213> Homo sapiens

<400> 117
Ile Pro Leu Ala Glu Met Glu Ala Leu Ser Leu Thr Ser Glu Ile Val
1 5 10 15
Ser Glu Pro Ser Cys Ser Leu Ala Leu Thr Asp Asp Ser Leu Pro Asp
20 25 30
Asp Met His Thr Leu Leu Leu Ser Ala Leu Glu Ser Asn
35 40 45

<210> 118
<211> 56
<212> PRT
<213> Homo sapiens

<400> 118
Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val
1 5 10 15

```
Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr
            20                  25                  30
Met Cys Arg His Gly Ser Thr Ala Glu Gly Pro Leu Gly His Arg Gly
        35                  40                  45
Trp Gly Leu Pro Lys Ala Gln Ser
    50                  55
```

<210> 119
<211> 57
<212> PRT
<213> Homo sapiens

<400> 119

```
Gly Ser Val Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser Tyr Ile
 1               5                  10                  15
Leu Gln Leu Pro Lys Asp Ala Pro His Leu Leu Gln Pro His Ser Ala
            20                  25                  30
Pro Thr Trp Gly Thr Ile Pro Lys Leu Pro Pro Pro Gly Arg Ser Pro
        35                  40                  45
Leu Ala Gln Arg Pro Leu Arg Arg Gln
    50                  55
```

<210> 120
<211> 22
<212> PRT
<213> Homo sapiens

<400> 120

```
Ala Ala Ile Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser Arg
 1               5                  10                  15
Glu Asp Leu Leu Ala Glu
            20
```

<210> 121
<211> 79
<212> PRT
<213> Homo sapiens

<400> 121

```
Val Ser Gly Pro Ser Pro Pro Leu Ala Arg Ala Tyr Ser Phe Trp Gly
 1               5                  10                  15
Gln Ser Ser Thr Gln Ala Gln Gln His Ser Arg Ser His Ser Lys Ile
            20                  25                  30
Ser Lys His Met Thr Pro Pro Ala Pro Cys Pro Gly Pro Glu Pro Asn
        35                  40                  45
Trp Gly Lys Gly Pro Pro Glu Thr Arg Ser Ser Leu Glu Leu Asp Thr
    50                  55                  60
Glu Leu Ser Trp Ile Ser Gly Asp Leu Leu Pro Pro Gly Gly Gln
65                  70                  75
```

<210> 122
<211> 143
<212> PRT
<213> Homo sapiens

<400> 122
Glu Glu Pro Pro Ser Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val Glu
1 5 10 15
Ala Gln Ser Cys Gln Arg Arg Pro Thr Ser Trp Leu Asp Glu Gln Arg
20 25 30
Arg His Ser Ile Ala Val Ser Cys Leu Asp Ser Gly Ser Gln Pro His
35 40 45
Leu Gly Thr Asp Pro Ser Asn Leu Gly Gly Gln Pro Leu Gly Gly Pro
50 55 60
Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro Pro Ser Ile Thr Ile Asp
65 70 75 80
Pro Pro Glu Ser Gln Gly Pro Arg Thr Pro Pro Ser Pro Gly Ile Cys
85 90 95
Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser Lys Asp Pro Leu Ala Ser
100 105 110
Gly Pro Pro Asp Ser Met Ala Ala Ser Pro Ser Pro Lys Lys Asp Val
115 120 125
Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro Ala Asp Leu Asp Pro
130 135 140

<210> 123
<211> 79
<212> PRT
<213> Homo sapiens

<400> 123
Met Ala Glu Ser Ala Ser Pro Pro Ser Ser Ser Ala Ala Ala Pro Ala
1 5 10 15
Ala Glu Pro Gly Val Thr Thr Glu Gln Pro Gly Pro Arg Ser Pro Pro
20 25 30
Ser Ser Pro Pro Gly Leu Glu Glu Pro Leu Asp Gly Ala Asp Pro His
35 40 45
Val Pro His Pro Asp Leu Ala Pro Ile Ala Phe Phe Cys Leu Arg Gln
50 55 60
Thr Thr Ser Pro Arg Asn Trp Cys Ile Lys Met Val Cys Asn Pro
65 70 75

<210> 124
<211> 37
<212> PRT
<213> Homo sapiens

<400> 124
Trp Phe Glu Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr
1 5 10 15
Leu Gly Met Tyr Gln Pro Cys Asp Asp Met Asp Cys Leu Ser Asp Arg
20 25 30
Cys Lys Ile Leu Gln
35

<210> 125
<211> 45
<212> PRT
<213> Homo sapiens

<400> 125
Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu Met Val Leu
1 5 10 15
Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr Leu Gly Asp
20 25 30
Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly
35 40 45

<210> 126
<211> 32
<212> PRT
<213> Homo sapiens

<400> 126
Met Val Glu Tyr Ser Leu Asp Leu Gln Asn Ile Asn Leu Ser Ala Ile
1 5 10 15
Arg Thr Val Arg Val Leu Arg Pro Leu Lys Ala Ile Asn Arg Val Pro
20 25 30

<210> 127
<211> 54
<212> PRT
<213> Homo sapiens

<400> 127
Ser Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu
1 5 10 15
Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly Ile
20 25 30
Ile Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu
35 40 45
Glu Glu Asn Phe Thr Ile
50

<210> 128
<211> 105
<212> PRT
<213> Homo sapiens

<400> 128
Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln Pro Glu Glu Asp Asp
1 5 10 15
Glu Met Pro Phe Ile Cys Ser Leu Ser Gly Asp Asn Gly Ile Met Gly
20 25 30
Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly Arg Glu Cys Cys Leu
35 40 45
Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly Arg Gln Asp Leu Asn
50 55 60
Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr Tyr Asn Val Cys Arg
65 70 75 80
Thr Gly Ser Ala Asn Pro His Lys Gly Ala Ile Asn Phe Asp Asn Ile
85 90 95
Gly Tyr Ala Trp Ile Val Ile Phe Gln
100 105

<210> 129
<211> 31
<212> PRT
<213> Homo sapiens

<400> 129
Val Ile Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp
1 5 10 15
Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
20 25 30

<210> 130
<211> 104
<212> PRT
<213> Homo sapiens

<400> 130
Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr
1 5 10 15
Gln Phe Ser Glu Thr Lys Gln Arg Glu His Arg Leu Met Leu Glu Gln
20 25 30
Arg Gln Arg Tyr Leu Ser Ser Ser Thr Val Ala Ser Tyr Ala Glu Pro
35 40 45
Gly Asp Cys Tyr Glu Glu Ile Phe Gln Tyr Val Cys His Ile Leu Arg
50 55 60
Lys Ala Lys Arg Arg Ala Leu Gly Leu Tyr Gln Ala Leu Gln Ser Arg
65 70 75 80
Arg Gln Ala Leu Gly Pro Glu Ala Pro Ala Pro Ala Lys Pro Gly Pro
85 90 95
His Ala Lys Glu Pro Arg His Tyr
100

<210> 131
<211> 35
<212> PRT
<213> Homo sapiens

<400> 131
His Gly Lys Thr Lys Gly Gln Gly Asp Glu Gly Arg His Leu Gly Ser
1 5 10 15
Arg His Cys Gln Thr Leu His Gly Pro Ala Ser Pro Gly Asn Asp His
20 25 30
Ser Gly Arg
35

<210> 132
<211> 142
<212> PRT
<213> Homo sapiens

<400> 132
Glu Leu Cys Pro Gln His Ser Pro Leu Asp Ala Thr Pro His Thr Leu
1 5 10 15
Val Gln Pro Ile Pro Ala Thr Leu Ala Ser Asp Pro Ala Ser Cys Pro
20 25 30

```
Cys Cys Gln His Glu Asp Gly Arg Arg Pro Ser Gly Leu Gly Ser Thr
        35                  40                  45
Asp Ser Gly Gln Glu Gly Ser Gly Ser Gly Ser Ser Ala Gly Gly Glu
    50                  55                  60
Asp Glu Ala Asp Gly Asp Gly Ala Arg Ser Ser Glu Asp Gly Ala Ser
65                  70                  75                  80
Ser Glu Leu Gly Lys Glu Glu Glu Glu Glu Gln Ala Asp Gly Ala
                85                  90                  95
Val Trp Leu Cys Gly Asp Val Trp Arg Glu Thr Arg Ala Lys Leu Arg
            100                 105                 110
Gly Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met Ala Ile
        115                 120                 125
Leu Val Asn Thr Val Ser Met Gly Ile Glu His His Glu Gln
    130                 135                 140
```

<210> 133
<211> 51
<212> PRT
<213> Homo sapiens

<400> 133

```
Pro Glu Glu Leu Thr Asn Ile Leu Glu Ile Cys Asn Val Val Phe Thr
 1               5                  10                  15
Ser Met Phe Ala Leu Glu Met Ile Leu Lys Leu Ala Ala Phe Gly Leu
            20                  25                  30
Phe Asp Tyr Leu Arg Asn Pro Tyr Asn Ile Phe Asp Ser Ile Ile Val
        35                  40                  45
Ile Ile Ser
    50
```

<210> 134
<211> 62
<212> PRT
<213> Homo sapiens

<400> 134

```
Ile Trp Glu Ile Val Gly Gln Ala Asp Gly Gly Leu Ser Val Leu Arg
 1               5                  10                  15
Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe Met Pro Ala
            20                  25                  30
Leu Arg Arg Gln Leu Val Val Leu Met Lys Thr Met Asp Asn Val Ala
        35                  40                  45
Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser
    50                  55                  60
```

<210> 135
<211> 39
<212> PRT
<213> Homo sapiens

<400> 135

```
Ile Leu Gly Met His Ile Phe Gly Cys Lys Phe Ser Leu Arg Thr Asp
 1               5                  10                  15
Thr Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp
            20                  25                  30
```

Ala Ile Val Thr Val Phe Gln
35

<210> 136
<211> 52
<212> PRT
<213> Homo sapiens

<400> 136
Ile Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly Met Ala
1 5 10 15
Ser Thr Ser Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met Thr Phe
20 25 30
Gly Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val Glu Gly
35 40 45
Phe Gln Ala Glu
50

<210> 137
<211> 31
<212> PRT
<213> Homo sapiens

<400> 137
Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser Ser Ser Asn
1 5 10 15
Ile Glu Glu Phe Asp Lys Leu Gln Glu Gly Leu Asp Ser Ser Gly
20 25 30

<210> 138
<211> 68
<212> PRT
<213> Homo sapiens

<400> 138
Asp Pro Lys Leu Cys Pro Ile Pro Met Thr Pro Asn Gly His Leu Asp
1 5 10 15
Pro Ser Leu Pro Leu Gly Gly His Leu Gly Pro Ala Gly Ala Ala Gly
20 25 30
Pro Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro Met Leu Val Ala Leu
35 40 45
Gly Ser Arg Lys Ser Ser Val Met Ser Leu Gly Arg Met Ser Tyr Asp
50 55 60
Gln Arg Ser Leu
65

<210> 139
<211> 157
<212> PRT
<213> Homo sapiens

<400> 139
Ser Ser Ser Arg Ser Ser Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala
1 5 10 15
Trp Ala Ser Arg Arg Ser Ser Trp Asn Ser Leu Lys His Lys Pro Pro

```
            20                  25                  30
Ser Ala Glu His Glu Ser Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala
        35                  40                  45
Arg Val Cys Glu Val Ala Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro
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65                  70                  75                  80
His Arg His Arg His His Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp
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Ser Val Asp Leu Ala Glu Leu Val Pro Ala Val Gly Ala His Pro Arg
            100                 105                 110
Ala Ala Trp Arg Ala Ala Gly Pro Ala Pro Gly His Glu Asp Cys Asn
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145                 150                 155
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<212> PRT
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<212> PRT
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<400> 146
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<210> 147
<211> 64
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<211> 51
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<213> Homo sapiens

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Gln Pro Thr
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<211> 37
<212> PRT
<213> Homo sapiens

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<210> 156
<211> 36
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<211> 55
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Gly Leu Ser Pro Ala Ala Arg Arg Arg Leu Ser Leu Arg Gly Arg Gly
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Leu Phe Ser Leu Arg Gly Leu Arg Ala His Gln Arg Ser His Ser Ser
65 70 75 80
Gly Gly Ser Thr Ser Pro Gly Cys Thr His His Asp Ser Met Asp Pro
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Ser Asp Glu Glu Gly Arg Gly Gly Ala Gly Gly Gly Gly Ala Gly Ser
100 105 110
Glu His Ser Glu Thr Leu Ser Ser Leu Ser Leu Thr Ser Leu Phe Cys
115 120 125
Pro Pro Pro Pro Pro Pro Ala Pro Gly Leu Thr Pro Ala Arg Lys Phe
130 135 140
Ser Ser Thr Ser Ser Leu Ala Ala Pro Gly Arg Pro His Ala Ala Ala
145 150 155 160
Leu Ala His Gly Leu Ala Arg Ser Pro Ser Trp Ala Ala Asp Arg Ser
165 170 175
Lys Asp Pro Pro Gly Arg Ala Pro Leu Pro Met Gly Leu Gly Pro Leu
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<211> 51
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50 55 60
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65 70 75 80
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100 105 110
Gly Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met Ala Ile
115 120 125
Leu Val Asn Thr Val Ser Met Gly Ile Glu His His Glu Gln
130 135 140

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 November 2000 (23.11.2000)

PCT

(10) International Publication Number
WO 00/70044 A3

(51) International Patent Classification[7]: C12N 15/12, C07K 14/705, G01N 33/68

(21) International Application Number: PCT/US00/12383

(22) International Filing Date: 8 May 2000 (08.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/134,063 13 May 1999 (13.05.1999) US
60/137,547 4 June 1999 (04.06.1999) US

(71) Applicant *(for all designated States except US)*: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; 111 Market Place, Baltimore, MD 21201 (US).

(72) Inventors; and

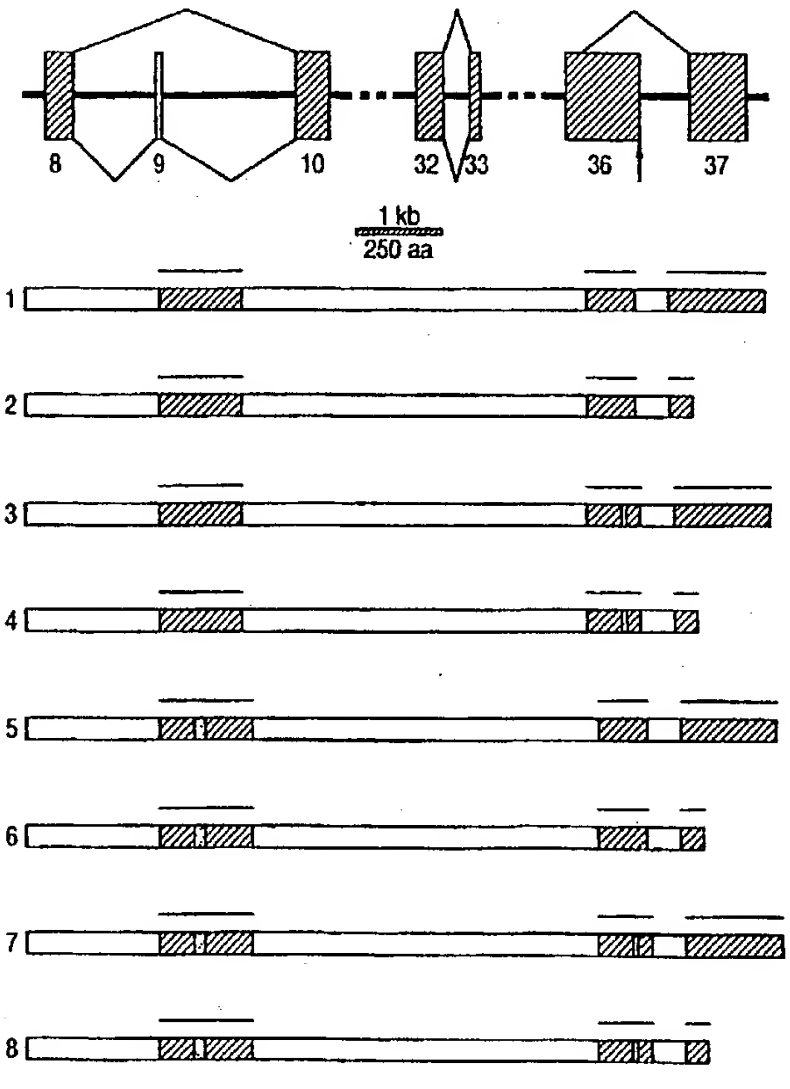
(75) Inventors/Applicants *(for US only)*: **MITTMAN, Scott** [US/US]; The Johns Hopkins University, 111 Market Place, Baltimore, MD 21201 (US). **AGNEW, William, S.** [US/US]; The Johns Hopkins University, 111 Market Place, Baltimore, MD 21201 (US).

(74) Agents: **KAGAN, Sarah, A.** et al.; Banner & Witcoff, Ltd., Eleventh Floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: HUMAN BRAIN T CALCIUM CHANNEL ALPHA-SUBUNIT SPLICE VARIANTS



(57) Abstract: The structures of *CACNA1G* and *CACNA1I*, the genes encoding the human brain T Ca^{2+} channel α_{1G} and α_{1I} subunits, respectively, were determined by comparison of polymerase chain reaction-amplified brain cDNA and genomic sequences. *CACNA1G* consists of at least 38 exons spanning at least 66,490 basepairs of chromosome 17q22. Alternative splicing of the RNA occurs at six sites: cassette exons 14, 26, 34 and 35, an internal donor in exon 25 and protein-coding intron 38B. Additionally, the RNA can be polyadenylated at either of two sites. Alternative splicing of *CANCA1G* RNA may lead to expression of as many as 64 distinct protein products, ranging from 2,171 to 2,377 amino-acids residues, with as many as 45 potential phosphorylation sites. *CACNA1I* consists of at least 37 exons spanning at least 116,390 basepairs of chromosome 22q12.3-13.2. Alternative splicing of the gene occurs at three sites: cassette exon 9, an alternative acceptor in exon 33 and mutually-exclusive 3' exons 36B and 37. Alternative splicing of *CANCA1I* RNA may lead to expression of as many as 8 distinct protein products, ranging from 1,968 to 2,223 amino-acids residues, with as many as 28 potential phosphorylation sites. Molecular diversity generated by alternative splicing and post-translation modification of these and other members of the T α_1 subunit gene family may account for the observed heterogeneity of T currents in central neurons.

WO 00/70044 A3

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
17 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Inter ional Application No
PCT/US 00/12383

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, EMBL, WPI Data, MEDLINE, EMBASE, SCISEARCH, BIOTECHNOLOGY ABS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEREZ-REYES EDWARD ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel." NATURE (LONDON), vol. 391, no. 6670, 26 February 1998 (1998-02-26), pages 896-900, XP002147614 ISSN: 0028-0836 abstract; figure 1 page 896, right-hand column, paragraph 3 --- -/--	1-5,11, 12,15, 16,19,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2000	22. 12. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gurdjian, D

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/12383

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5, 11, 12, 15,16,19, 20

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/12383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CRIBBS LEANNE L ET AL: "Cloning and characterization of alphalH from human heart, a member of the T-type Ca2+ channel gene family." CIRCULATION RESEARCH, vol. 83, no. 1, 13 July 1998 (1998-07-13), pages 103-109, XP000938541 ISSN: 0009-7330 abstract; figure 1 ---	1-5,11, 12,15, 16,19,20
X	DATABASE EMBL [Online] Accession number ab012043, 8 January 1999 (1999-01-08) KISHI F.: "Homo spaiens mRNA for NBR13" XP002147615 abstract ---	4,5
X	-& DATABASE TREMBL [Online] Acession number 094770, 1 May 1999 (1999-05-01) KISHI F.: "Human NBR13" XP002147616 abstract ---	4,5
A	WILLIAMS M E ET AL: "Cloning and characterization of a novel human Ca2+ channel alphal subunit associated with a low-voltage activated (LVA) Ca2+ channel." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 24, no. 1-2, 1998, page 1823 XP000938545 28th Annual Meeting of the Society for Neuroscience, Part 2;Los Angeles, California, USA; November 7-12, 1998 ISSN: 0190-5295 the whole document ---	1-5,11, 12,15, 16,19,20
A	WILLIAMS MARK E ET AL: "Structure and functional characterization of a novel human low-voltage activated calcium channel." JOURNAL OF NEUROCHEMISTRY, vol. 72, no. 2, February 1999 (1999-02), pages 791-799, XP000938528 ISSN: 0022-3042 the whole document ---	1-5,11, 12,15, 16,19,20

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/12383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEE JUNG-HA ET AL: "Cloning and expression of a novel member of the low voltage-activated T-type calcium channel family." JOURNAL OF NEUROSCIENCE, vol. 19, no. 6, 15 March 1999 (1999-03-15), pages 1912-1921, XP000946046 ISSN: 0270-6474 the whole document ---	1-5,11, 12
P,X	MITTMAN S ET AL: "Structure and alternative splicing of the genes encoding the human brain T Ca2+ channel subunits alpha1G and alpha1I." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 25, no. 1-2, 1999, page 197 XP000938544 29th Annual Meeting of the Society for Neuroscience, Part 1;Miami Beach, Florida, USA; October 23-28, 1999 ISSN: 0190-5295 the whole document ---	1-5,11, 12
P,X	MITTMAN SCOTT ET AL: "Structure and alternative splicing of the gene encoding alpha1G, a human brain T calcium channel alpha1 subunit." NEUROSCIENCE LETTERS, vol. 274, no. 3, 29 October 1999 (1999-10-29), pages 143-146, XP000946163 ISSN: 0304-3940 the whole document ---	1-5,11, 12
P,X	CRIBBS LEANNE L ET AL: "Molecular cloning and functional expression of Cav3.1c, a T-type calcium channel from human brain." FEBS LETTERS, vol. 469, no. 1, 21 January 2000 (2000-01-21), pages 54-58, XP000938714 ISSN: 0014-5793 the whole document ---	1-5,11, 12
P,X	MONTEIL ARNAUD ET AL: "Molecular and functional properties of the human alpha1G subunit that forms T-type calcium channels." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 9, 3 March 2000 (2000-03-03), pages 6090-6100, XP000938755 ISSN: 0021-9258 abstract; figures 2,3 ---	1-5,11, 12

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/12383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 29847 A (UNIV LOYOLA CHICAGO ;CRIBBS LEANNE L (US); PEREZ REYES EDWARD (US)) 17 June 1999 (1999-06-17) figures SEQ.1-11; example 1 -----	1-5,11, 12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/12383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9929847 A	17-06-1999	EP 1036170 A	20-09-2000